SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 88 FEBRUARY, 1949 NUMBER 2

VAGINAL AND OVARIAN METASTASES FROM HYPERNEPHROMA

Report of Case and Review of Literature

KARL H. MARTZLOFF, M.D., F.A.C.S., and CHARLES H. MANLOVE, M.D.,
Portland, Oregon

SO-CALLED hypernephroma of the kidney is no rarity and in itself would warrant no special comment. The following case of left renal hypernephroma, however, is reported because of several unusual aspects, viz.: (1) the first clinical symptom was vaginal bleeding from vaginal metastases, (2) left ovarian metastasis occurred without demonstrable evidence of defeminization or virilization, and (3) the patient lived 2½ years after the onset of her original symptoms and represents the 23rd reported instance of this unusual complication (Fig. 1).

No attempt will be made to discuss the debatable question of the histogenesis of the tumors which are generally included under the term hypernephroma. The tumor in our case, described in more detail later, has been so designated because its component cells were large, clear, pale, well delineated structures which generally characterize this group of renal tumors.

CASE REPORT

Mrs. H. S., white, aged 57 years, primipara, was first seen December 3, 1945, and died December 12, 1947. Her family and personal history were irrelevant. Menstruation ceased in 1937 or 1938. No vaginal bleeding or unusual discharge occurred until the onset of the present illness, July 15, 1945, when there occurred a spontaneous, bright red vaginal discharge. No other symptoms were noted and the patient felt otherwise well. Diagnostic curettage was done on July 16, 1945. The result of the histologic study is not known. Panhysterectomy was performed August 17, 1945; the tubes and ovaries were reported to have been left *in situ*. At this time a "small black growth" present in the vagina was removed but no histologic study was recorded. A growth of similar appearance, and in a similar location was again noticed and removed on October 15, 1945. The pathologist was reported to have been unable to make a definite diagnosis but he did not consider the microscopic picture indicative of cancer. During the entire interval the patient's vaginal bleeding continued in varying amount, with episodes so severe that obvious anemia and weakness ensued. When first seen by one of us (K. H. M.) in December 1945, because of vaginal hemorrhage, no noteworthy weight loss had occurred.

Physical examination was made December 3, 1945. In the vagina was found a marked accumulation of secretion and a hyperemia due to the presence of a large vaginal pack placed there several days previously by patient's former physician. Vaginal tenderness was so marked that observation was unsatisfactory. It could be seen, however, that the cervix uteri was absent. Three small, discrete, red nodules, 2 to 5 millimeters in diameter, could be fairly distinctly recognized in the left half of the vagina. One of these bled freely. Bimanual abdominovaginal and rectal examinations revealed the firm character of the previously noted nodules and confirmed the absence of the entire uterus.

At examination one week later the vaginal inflammation had markedly lessened and the previously

From the Departments of Surgery and Pathology, University of Oregon Medical School, and the Surgical and Pathological services of the Good Samaritan Hospital.

noted nodules were all bleeding. Careful visualization of the vagina was again difficult.

On December 26, 1945, following hospitalization, complete physical examination was unimportant except for palpation of a large, normally movable left kidney. The urine on this and repeated examinations showed blood. However, only one of the specimens was obtained by catheter.

On December 27, 1945, at speculum examination done under gas anesthesia, absence of the cervix was verified and four nodules were identified (Fig. 2), viz.: (1) a profusely bleeding one about 1 centimeter in diameter on the left posterior or posterolateral wall about 3 centimeters within the introitus; (2) a smaller nodule on the right anterolateral wall near the introitus; (3) one on the right lateral wall midway between introitus and vault; (4) one on the left lateral wall near the introitus. All but one of these were excised with the endothermy unit for biopsy and the bases of all were coagulated. Recovery was uneventful. Intravenous pyelographic study now revealed not only left renal enlargement but moderate hydronephrosis, medial displacement of the ureter, and distortion of the inferior calyces sufficiently characteristic to warrant the diagnosis of an inferior pole renal tumor. Patient returned home to await the result of the microscopic examination of the paraffin sections and the decision as to the best method of treatment of the left kidney disease. Histologic study of the vaginal nodules revealed a bizarre picture for a growth located in the vagina, namely the structure of so-called hypernephroma (Figs. 3 and 4).

The clinical impression was malignant nephroma of the inferior pole of the left kidney, with vaginal metastases which were the source of serious vaginal hemorrhage.

The patient was seen again January 25, 1946. All previously described vaginal areas were healed and felt elastic except for the left posterolateral area (Fig. 2, area *1*) near the introitus which felt indurated. In addition there was a previously unobserved small nodule (Fig. 2, area *5*) possibly 1 centimeter in diameter in the left anterior vaginal fornix. This was dark blue in color, smooth surfaced, firm in consistency, and movable. Previous observations were confirmed. X-ray study revealed no recognizable evidence of metastases in the thoracic cavity, thoracic cage, shoulder girdle, dorsolumbar spine, or ilium. The dubious outlook was discussed with the patient's family who felt that nephrectomy should be recommended to the patient.

X-ray studies on February 11, 1946, again showed no metastases. An anterior extraperitoneal nephrectomy through a long, left, semilunar line incision was done on February 12, 1946. The left kidney with its tumor (hypernephroma) together with tumor tissue surrounding the ureter near the hilus and a segment of adjacent involved (verified histologically) posterior peritoneum were removed without event despite the adherence and marked vascularity of the tissues about the tumor. The entire exposure particularly the access to the renal pedicle under direct vision and without undue mobilization proved essentially ideal with this approach. Recovery was uneventful, the patient was ambulant on the fourth postoperative day, and on February 19, 1946 the nodule in the left anterolateral vaginal fornix was removed. This growth was histologically similar to the others. The operative wound was electrocoagulated and the area on the left posterolateral wall again coagulated. Recovery was uneventful.

Abdominal examination, April 24, 1946, revealed no pertinent data. Speculum examination showed a small, flat red area in the left fornix and a purplish red tumefaction possibly 1 centimeter in diameter on the left posterolateral aspect of the introitus (Fig. 2, area *6*). This bled readily following slight trauma and was excised (May 7, 1946) with a wide margin of normal tissue. The base of this wound and the area in the left fornix were coagulated. The excised tumor was histologically similar to the others. Recovery was uneventful.

July 10, 1946, a mass was palpated in the left pelvis. Patient felt well and was doing her housework at this time. Previous abdominopelvic examination had been done January 25, 1946. The mass was firmly elastic, smooth, and rather freely movable with the vaginal vault. This observation was confirmed on September 12, 1946, although the mass had enlarged somewhat, now measuring possibly 8 to 10 centimeters in diameter. Examination was otherwise negative as were x-ray studies for metastases on September 11. The mass was considered ovarian in origin. The possibility that it might represent a manifestation of tumor metastasis was regarded as an obvious possibility. Laparotomy was done on October 1, 1946. The condition of the right tube and ovary was normal. The uterus was absent and the peritoneal surfaces, except for a few adhesions, appeared normal. A left sided retroperitoneal mass attached to the left infundibulopelvic ligament and occupying the customary position of a retroperitoneal ovarian tumor was removed without difficulty. Histologically this mass proved to be similar in structure to the original renal neoplasm. Bleeding from veins on the posterolateral pelvic wall was a serious complicating factor, causing profound shock. Bleeding was completely controlled and closure was done without drainage. Palpation and inspection in the general region of the previously removed left kidney disclosed nothing pertinent, but no further exploration was done because of the blood loss. Patient left hospital on the 12th postoperative day and was again subjectively well.

December 16, 1946 a nodule (Fig. 2, area *7*) 4 millimeters in diameter was noted on right anterior vaginal wall at the introitus 1 centimeter from the external urethral meatus. This had a pink base and purplish apex (Fig. 1). It was smooth, firm, fixed to the mucous membrane but movable over the underlying structures and was excised with an endothermy unit January 28, 1947. The specimen measured 1.2 by 0.8 by 0.7 centimeter. The patient when last seen in April, 1947, showed possible evidence of recurrence.

Fig. 1. Metastatic hypernephroma nodule on right vestibulum vaginae. This was last vaginal nodule observed and excised. Figure 2, spot 7, represents this tumor.

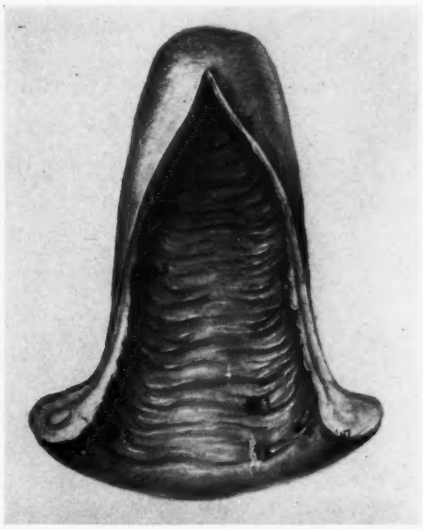

Fig. 2. Diagrammatic representation of location of vaginal hypernephroma metastases. Nodules 1 to 4 were observed December 27, 1945; nodule 5, January 25, 1946; nodule 6, (possibly remanifestation of nodule 1) April 24, 1946; nodule 7, December 16, 1946.

She felt weak and appeared ill but without definite weight loss. Palpation revealed a definite sense of fullness in the left flank. The blood sedimentation rate was 49 millimeters in 45 minutes in May, 1946, and continued moderately but definitely accelerated. She subsequently developed a hemiplegia and a definitely palpable mass was noted in the left flank. She died December 12, 1947, 29 months from the time of the first symptom—vaginal bleeding.

Gross examination of the specimen. The metastatic vaginal nodules for purposes of brevity will not be described in detail. Their cut surfaces were firm and showed gray and white striations. Some areas showed rather large blood containing channels.

The left kidney (Fig. 9) in its fixed state measured 15 by 8.5 by 7 centimeters. The surface was rough and its inferior half was occupied by a somewhat nodular enlargement which appeared everywhere encapsulated except at a point on its medial aspect where the capsule was broken. On section the pelvis showed obvious though moderate hydronephrosis and in its inferior portion distortion by the tumor. The sectioned tumor surface appeared gelatinoid with areas of softening and hemorrhage, and was generally of a light yellowish color with areas of deeper yellow and elsewhere areas that were light brown.

The renal vein on careful dissection showed no demonstrable tumor invasion. The left pelvic tumor was a round, well encapsulated mass which in its fixed state measured 6.3 centimeters in diameter. In cross section there was a central zone of softened, liquefying, pink material. The more solid, though spongy, peripheral portions showed a yellowish coloration with radiating red and pink striations. There was a capsule about 2 millimeters thick. The fallopian tube could not be definitely recognized in the gross though its presence was verified histologically.

Histology. The histology of all the tumor tissue was similar to that of the renal tumor which has been described. This was composed of large compact alveoli filled with large polyhedral cells with distinct cell outlines. The cytoplasm was abundant, generally clear but often contained some fine pink staining particles. The nuclei were generally round and varied moderately but definitely in size and staining reaction. The chromatin was moderately to coarsely granular, stained deeply, and lay in a comparatively pale blue to clear nuclear matrix. Nucleoli were almost uniformly present. Mitoses were infrequent. The fibrous matrix comprising the supporting structure of the tumor was composed of fine strands of connective tissue varying from one to several cells in thickness. Blood vessels per se were practically absent.

There was a general tendency for central degeneration to occur in these cell masses so that some had the appearance of glandular alveoli. Many of these contained central areas of hemorrhage. Some were lined with a single layer of tumor cells without evidence of degenerative change. Here the alveolar space was occupied by normal appearing red blood

Fig. 3. Vaginal mucosa and underlying tumor. This represents spots *2*, *3*, or *4* in Figure 2. Specimens were not separately labeled at time of removal.

cells and had the appearance of a vascular channel. Viable tumor tissue was generally visible only at the periphery of the neoplasm; elsewhere there was necrosis. In fact, necrosis was so general that blocks for good sections were difficult to obtain.

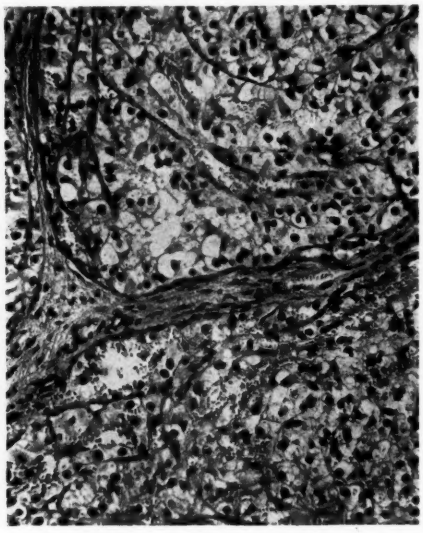

Fig. 4. High power from tumor area in Figure 3.

Fig. 5. Vaginal nodule showing tumor emboli in veins.

The vaginal metastases differed from the foregoing only in that overlying stratified vaginal epithelium was generally present. In some sections this was intact, in others there was overlying ulceration where the neoplasm had reached the surface. Tumor emboli could not generally be identified. However, an occasional blood vessel (vein) was seen showing unmistakable tumor embolus (Figs. 5 and 6). Vascular spaces lined with a single layer of tumor cells, as previously described, were common and undoubtedly account for the profuse hemorrhage that occurred when the tumor ulcerated through the vaginal mucosa. They might also be the source of tumor cell emboli and might explain metastatic phenomena when invasion of renal veins was not demonstrable.

Sections of the left pelvic tumor differed only from the foregoing in that ovarian stroma with a corpus albicans (Fig. 7) and the fallopian tube showing tumor infiltration of its external muscularis were recognizable at the periphery of the tumor.

Autopsy findings which are given in barest outline revealed a left retroperitoneal tumor occupying site of previously removed left kidney and extending from lower pole of the spleen into left pelvis to apex of the vaginal vault. The vaginal mucosa is smooth and shows no tumor. The left adrenal gland lies in close apposition to the tumor mass but shows no neoplastic involvement. The inferior vena cava shows tumor which extends superiorly for 8 centimeters from site of the left renal vein.

Metastases are found in the right kidney cortex, spleen, lungs, brain and myocardium of the left posterior ventricle.

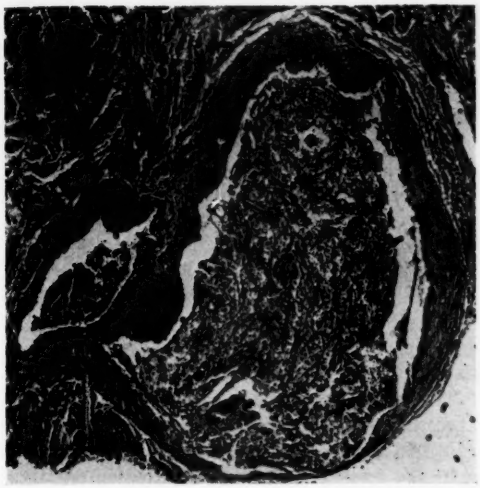

Fig. 6. High power of blood vessels with tumor emboli in Figure 5.

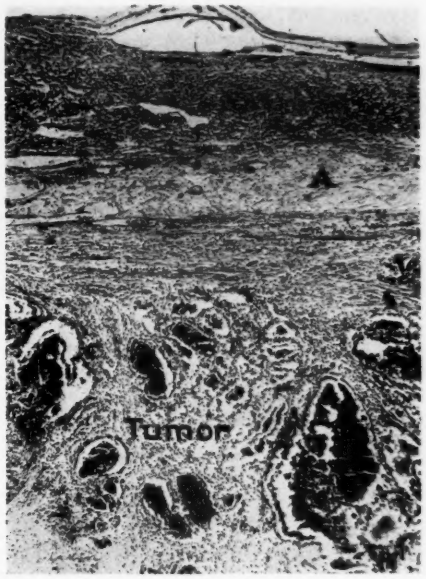

Fig. 7. From left ovary. Corpus albicans at *A*. Histology of tumor similar to that shown in Figures 3 and 8.

DISCUSSION

The occurrence of hypernephromatoid structures in the vagina either as fetal rests or as metastatic phenomena from a malignant tumor of similar character is rare. Deming, in a study of 29 patients with metastases from renal tumors, reports no metastases to ovaries or vagina. Eleven of the tumors were hypernephromas and 5 were adenocarcinomas. In a review of 46 ectopic adrenal rests (not metastases) Lasher describes none occurring in the vagina. Likewise, Nalle, in a study of 58 renal neoplasms and their metastases, encountered no vaginal or ovarian metastases.

Wynne states that about 20 instances of vaginal metastases from nephromas have been reported. Novak considers them extremely rare. Wharton describes two instances of vaginal metastases from renal tumor. In one of these the vaginal tumor which occurred in the vestibule was the first direct proof of the existence of renal tumor, thereby simulating Gragert's case.

It is understandable that when metastases become widespread as in the 4 cases reported by Sharnoff and Sala, vaginal metastases as late antemortem phenomena are probably not rare. No doubt they would be recognized more frequently if sought at autopsy.

Most writers attribute to Henke the first reported case of vaginal metastases from a

Fig. 8. High power of tumor area in Figure 9.

hypernephroma. Sharnoff and Sala state that Henke's patient was 69 years old, that autopsy showed hypernephroma of the left kidney, and that in both the renal and vaginal tumors the histologic picture was identical. As a matter of fact, Henke's report is a fragmentary 11 line statement, without illustrations and without detailed histologic description. It does not state which kidney was involved in the hypernephroma and it gives the patient's age as 60 years.

In all likelihood the case reported by Hoffmann is the same as the one reported by Henke, although all writers have considered each of these as being separate. Henke's report as previously noted is brief, fragmentary, and gives no details. Hoffmann's report is complete and states that Henke examined the tissue from his case and reported his observations. Additionally in each instance the patient was 60 years of age and had a metastatic skin tumor which showed hypernephroma cells on biopsy. Hoffmann specifically states that this tumor was located in the right thigh and the renal tumor demonstrated at autopsy in the left kidney. There is little danger of error, therefore, in considering these two reports as concerning the same patient.

The case reported by Overy is also generally accepted by writers on this subject. Overy's case is reported in a discussion of a paper by Doran. He describes an instance of his own in which a patient with a right sided abdominal mass developed a polypoid tumor on the anterior vaginal wall. This tumor was removed, recurred, and was again removed. No histologic studies were made of these tumefactions. The patient died 1 month later and a hypernephroma was found at autopsy. Overy does not state on which side the tumor was located. It is difficult in the absence of histological verification to see how this case can be considered as an instance of vaginal metastasis from a hypernephroma.

Reference to Table I reveals that, including our patient, 23 instances of hypernephromatous vaginal metastases have been reported. As in our patient the overwhelming majority (18) have occurred in the presence of left renal tumors. This combination has raised some questions, namely, are left sided tumors more frequent than right sided ones? If left sided tumors show a predilection for vaginal metastases, what is the explanation? To answer the first question it may be said that malignant renal tumors in adults occur probably more frequently on the right side. Lubarsch states that 321 of Kuesters 607 collected cases of malignant renal tumors occurred on the right and 272 on the left; while of 169 similar tumors collected by Albarran and Imbert, 90 occurred on the right and 74 on the left side. Deming reports that among 82 malignant renal tumors studied, 53 occurred on the right side. In this same study he found that men were afflicted about 2.5 times more frequently than women.

When malignant renal tumors are segregated according to histologic types, all of Lubarsch's compilations for hypernephromas show that men are again more frequently affected than women in a general ratio of about 2 to 1. However, when the side affected is considered there appears to be only a slight preponderance of lesions on the left side, the general ratio being about 1.3 to 1.

Therefore, if it is accepted that hypernephromas occur with possibly slightly greater frequency in the left kidney, then it is not mere coincidence that the overwhelming preponderance of vaginal metastases occur only in the presence of left renal tumors.

The major constant circulatory difference between the two kidneys occurs in the communication of the left spermatic (ovarian) vein with the left renal vein and the comparative shortness of the right renal vein and left renal artery. In view of the well recognized tendency for hypernephromas to invade the renal veins, it seems a fair assumption that the left ovarian vein offers the avenue by which the ovarian involvement occurred in our patient and by which vaginal involvement occurs in the majority of reported instances.

The occasional reported instance of uterine involvement is also probably similarly explainable. The free anastomosis between the left ovarian vein, the pampiniform plexus, the uterovaginal venous plexus and its more distal anastomoses as shown by Kownatzki and others, offers a logical explanation for the vaginal dissemination of the tumor in our case. The demonstration of venous tumor emboli in

the vaginal metastases in our patient offers support to this explanation, as opposed to a possible lymphatic mode of spread which is espoused by some authors. The theory of implantation on the vaginal mucosa of tumor cells passed in the urine as suggested by Sharnoff possesses little if any corroborative evidence.

One cannot help but entertain the suspicion that if the theory is correct that the left spermatic (ovarian) vein offers the route for retrograde metastasis of hypernephroma to the vagina then it should follow logically that left testicular metastasis must occur with equal or possibly greater frequency in men afflicted with left sided hypernephroma and would be recognized if looked for.

According to this and similar studies hypernephroma metastases to the vagina may be considered as rare lesions. We suspect, however, that their rarity is overevaluated. Similar instances undoubtedly occur, are recognized, but are not reported. The 2 cases mentioned by Wharton illustrate this point.

All patients in this study with the exception of Gragert's patient, Fleischmann's second case, and our patient died within 24 months following the recognition of the vaginal lesion. Fleischmann's and Gragert's patients both deserve special comment. The diagnosis of hypernephromatoid tumor was made on biopsy of the vaginal tumor of Gragert's patient. However, it was not definitely determined whether this represented a benign or a malignant process. The patient was seen again 16 months later with the story of having noted a left sided abdominal swelling for 6 months. Pyelographic studies were negative but left nephrectomy revealed a hypernephroma. The patient was living and well 4 months after the nephrectomy and 21 months from the time of the original biopsy of the vaginal tumor.

Fleischmann's second patient was seen January 9, 1918, for vaginal bleeding from a small ulcerated nodule which was removed from the left posterior vaginal wall. Definite diagnosis was not made from the biopsy and the lesion was considered as a possible "adenoma sebaceum." Three months later a left lumbar tumor was discovered when patient was examined for left hypochondriac pain. Left nephrectomy was done 5 months later following deep x-ray therapy, and several new vaginal nodules were also removed. The renal tumor was a hypernephroma, and the vaginal nodules were recognized as similar to the renal lesion. Intermittent x-ray therapy was given to local and remote remanifestations of the disease. Death occurred May, 1923, 4 years 8 months after the lesions were recognized as hypernephroma.

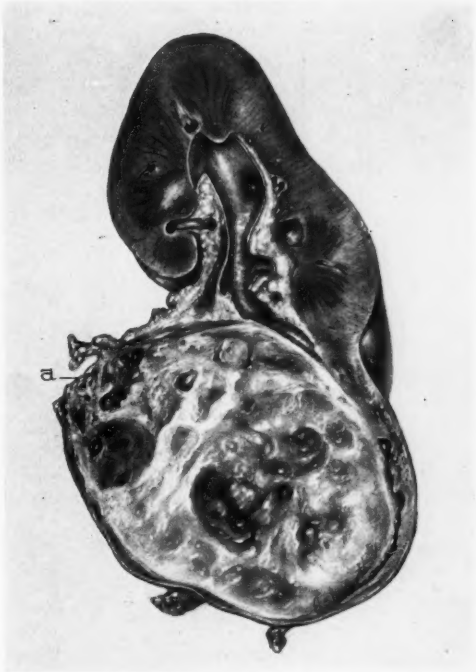

Fig. 9. Longitudinal section of left kidney with inferior pole neoplasm. Tumor had perforated capsule at *a* and involved parietal peritoneum.

In view of the foregoing and since an occasional patient comes to autopsy and reveals no other metastases than the vaginal lesion as illustrated by Graefenberg's first case, it appears justifiable to operate in such instances provided no other signs of metastases are demonstrable. Furthermore, on the basis of the experiences of Gragert, of Fleischmann in his second case, of Graefenberg in his first case, of Hirsch-Hoffmann, and of our own experience, one is led to the conclusion that, in the absence

TABLE I.—SUMMARY OF REPORTED CASES OF HYPERNEPHROMA METASTASES TO VAGINA*

Author	Date	Original clinical symptoms	Original vaginal metastasis, number and site	Hematuria	Age	Approximate duration of symptoms prior to diagnosis	Duration of life after diagnosis	Side of involved kidney. Remarks
1. Peham	1906	Vaginal bleeding	Single. Anterior left, along urethra	+	59	Several months	Not stated	Clinically a left kidney tumor. Not removed. Pt. alive at time of demonstration
2. Hoffmann	1907	?	Multiple growths at introitus urethrae, also posterior vaginal wall	+	60	6 months	?	Autopsy: left hypernephroma. Numerous other metastases including bladder
Henke	1906							Same case reported by Hoffmann. See text
3. Doran	1907	None referable to vagina	Multiple (5).	?	40	?	3 months	Right nephrectomy for hypernephroma. Vaginal lesions diagnosed after nephrectomy. Autopsy: metastases in liver and lungs
Overy	1907	?	Single, anterior. No histologic study	?	?	See text	—	Fragmentary report given in a discussion. Autopsy diagnosis hypernephroma. Does not state side. Metastases in liver and lungs
4. Freund	1908	Vaginal bleeding	Single. Anterior left wall at side of urethra	—	56	6 months	?	"Sarcomatous" left kidney removed 1½ years before vaginal tumor biopsy showed hypernephroma
5. Graefenberg	1908	Postmenopausal bleeding	Single. To left of clitoris	—	65	12 months		Died postop. pneumonia following removal of vaginal tumor for biopsy. Autopsy: left renal hypernephroma not previously suspected. No other metastases
6. Graefenberg	1908	—	Two. Anterior and posterior vagina, just within introitus	—	54	?	?	Vaginal tumor, hypernephroma. Clinically a left subcostal tumor, not confirmed by operation or autopsy. Questionably acceptable case
7. Fleischmann	1915	Vaginal bleeding	Multiple (3). Posterior fornix	—	62	17 days	?	Clinically, question of a left sided abdominal tumor. No operation. No autopsy. Vaginal tumors showed hypernephroma
8. Latzko	1918	No comment	—	—	—	—	—	Brief report. Pt. had left nephrectomy ¾ yr. before for hypernephroma. Vaginal tumors showed similar neoplasm
9. Gellhorn	1918	Abdominal pain. Left sided mass	Multiple (2). Anterior midline	?	54	?	2–3 days	Autopsy: left superior pole hypernephroma
10. Gragert	1927 1929	Vaginal bleeding, postmenopausal	Single. Left anterior vaginal wall	—	53	6 months	21 plus months	Left nephrectomy for tumor noticed 17 mos. after vaginal biopsy and 23 mos. after first symptom. Pt. living at time of last report, 1929
11. Hirsch-Hoffmann	1928	Vaginal bleeding, postmenopausal	Single. Anterior vagina at external urethral meatus	o	71	Probably 6 months	4 months	No renal tumor felt. No operation. Autopsy: left hypernephroma with metastases
12. Fleischmann	1929	Vaginal bleeding	Single. Left posterior near introitus	o	50	8 months	4 years, 8 mos.	Left hypernephroma (see text)
13. Szymonowicz	1932	Left hypochondriac pain. Hematuria	Single. Left labium minus at external urethral meatus	+	56	2½ months	?	Diagnosis made on tissue from left vulva. No autopsy. No operation on kidney. Left (?) kidney tumor
14. Bowes	1935	Vaginal discharge. Vulval tumor	Single, left suburethral	?	52	8 weeks	2 years?	Nephrectomy for left lower pole hypernephroma
15. Sharnoff and Sala	1936	Tender lump in back	Single, anterior wall behind external urethral meatus	+	65	?	Died 18 mo. after first symptom began	Left hypochondriac mass. X-ray distortion left renal pelvis. No operation. No autopsy. Vaginal biopsy, hypernephroma

*See footnote at end of table.

TABLE I.—SUMMARY OF REPORTED CASES OF HYPERNEPHROMA METASTASES TO VAGINA*—Continued

Author	Date	Original clinical symptoms	Original vaginal metastasis, number and site	Hematuria	Age	Approximate duration of symptoms prior to diagnosis	Duration of life after diagnosis	Side of involved kidney. Remarks
16. Sharnoff and Sala	1936	Abdominal mass	Single, anterior wall behind external urethral meatus	?	Not given	5–6 months	6–7 months	Autopsy: left hypernephroma
17. Sharnoff and Sala	1936	Hematuria	Single, right labium minus	?	57	2 years	18 days	Autopsy: right hypernephroma and other metastases
18. Sharnoff and Sala	1936	Mass in upper left abdomen	Mass filling right vaginal fornix	?	51	16 months?	3 months	Left nephrectomy attempted, not successful. Biopsy of renal tumor: hypernephroma
19. Pardella	1936	Left sided tumor	Left vulva and vagina	0	50	12 months	6 months	Left nephrectomy for hypernephroma. Autopsy: other metastases present
20. Manzoni	1936	Vaginal bleeding. Right inguinal tumor	Single. Ant. vagina.	0	56	?	?	Left nephrectomy for renal tubular carcinoma. Vaginal tumor and right inguinal node similar histology
21. Taussig	1938	Vaginal bleeding	Single. Left anterior wall, suburethral	0	42	3 weeks	?	Nephrectomy for left hypernephroma. Patient living at time of demonstration
22. Kurzrok and Fenichel	1942	Cough and chest pain, 6 months	Single. Anterior right vaginal wall	0	49	6 months	4 months	No autopsy. No nephrectomy. Palpable left kidney. Pyelography: slight elongation left upper calyx. Histologic diagnosis vaginal tumor: vaginal cancer, metastatic from hypernephroma
23. Martzloff and Manlove	1948	Vaginal bleeding	Multiple, scattered	? See text.	57	5 plus months	23 plus months	Nephrectomy for left lower pole hypernephroma. Lived 29 mos. from onset of symptoms

*Cases have been considered acceptable for tabulation if vaginal lesion showed histologic appearance of hypernephroma although suspected kidney may not have been removed.

of any other conclusive signs and symptoms, if a hypernephromatoid lesion is demonstrated in the vagina, one would be sufficiently certain in suspecting the presence of a left hypernephroma to warrant surgical exploration of the left kidney.

Radiation therapy as used in treating some of the patients reported in the literature covered by this study, with the possible exception of Fleischmann's patient, did not appear to be of material benefit.

Numerous authors place considerable stress on the apparent predilection of the hypernephromatous vaginal metastases to appear on the left anterior vaginal wall near the external urethral meatus, and they are of the opinion that bleeding from this source may be the first sign of mischief. Reference to Table I reveals that of the 23 cases tabulated, 11 patients complained of vaginal bleeding as an original symptom; 8, however, apparently did not bleed and in 4 no statement is reported.

The anterior vaginal wall of the region near the external urethral meatus was the site of a single primary metastatic tumor 12 times. This tumor appeared to the left of the midline in 8 instances, to the right in 1 and apparently at the midline in 3. Probably no further generalizations can be drawn other than, as pointed out by Taussig, tumors which metastasize to the vagina, presumably via the blood stream, often show a predilection for localization in the distal vagina and frequently in its anterior aspect near the external urethral meatus.

SUMMARY

A case is reported in which bleeding from vaginal metastases was the first symptom of an unsuspected left renal hypernephroma. The case presumably represents the 23rd instance of vaginal metastases complicating hypernephroma reported in the literature. The complication is generally limited to tumors, of the left kidney, although exceptions are reported.

All patients with hypernephroma complicated with vaginal metastases, whose ultimate outcome is known, died as the result of the

hypernephroma with the exception of those who died at operation. It is assumed and we offer a corroborative observation that metastases ordinarily occur via venous channels. Communication of the left ovarian vein with the left renal vein proximally and the pampiniform plexus and uterovaginal plexus distally explain the peculiar predilection for vaginal metastases to occur with tumors of the left kidney. The suggestion is offered, therefore, that if the venous theory of dissemination is correct, then left testicular metastases should occur in men afflicted with a left hypernephroma.

This analysis also suggests that in the event a hypernephromatoid vaginal metastasis is diagnosed in a patient who shows no other demonstrable or conclusive evidence of renal tumor an exploration of the left kidney becomes a logical and therefore justifiable procedure.

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VESICOVAGINAL FISTULA AND ITS MANAGEMENT

With a Description of an Intravesical Operation for Certain Difficult Cases

LOUIS E. PHANEUF, M.D., Sc.D., F.A.C.S., and ROGER C. GRAVES, M.D., A.B., F.A.C.S.,
Boston, Massachusetts

VESICOVAGINAL fistula, with its resulting urinary incontinence, is one of the most distressing conditions afflicting womankind. The discovery of an operation to cure this malady remains one of the epochs in the history of medicine. Credit for the first successful operation has been given to J. Marion Sims when he closed Anarcha's fistula at the thirtieth operation, in May, 1849. Sims' (8) paper was published in 1852, although he had begun his experiments with this condition in 1845. His many failures were attributed to his suture material, usually silk, because the sutures would not hold. Similar failures were reported by other surgeons, although George Hayward (2, 3), of Boston, had reported a successful operation in 1839 and two others in 1851. In 1857 Sims (9) delivered an address before the New York Academy of Medicine in which he stated that "Silver as a suture is the greatest surgical achievement of the nineteenth century." In this address he claimed the honor of this discovery for his country. An editorial in the *New England Journal of Medicine* of November 22, 1945, however, declared that gilded silver wire sutures had been used by Mr. Montague Gosset, a surgeon of London, in January, 1934, in the closure of a vesicovaginal fistula and had achieved complete success. The editorial stated that: "Recently a unique copy of his address in 1857 was found in the joint library of the Harvard Medical School and the Harvard School of Public Health." This pamphlet, as noted on the cover, was sent by Dr. Nathan Bozeman, an early associate of Dr. Sims in Montgomery, Alabama, to Dr. George Hayward, of the Massachusetts General Hospital. Hayward wrote opposite the passage quoted above in which Sims claimed the honor for his country, "The silver suture was used in London in 1834 in vesicovaginal fistula with success and the case was published in the *Lancet*." One finds the article referred to by Hayward in the November 29, 1834 issue of the *Lancet*. Mr. Montague Gosset, a surgeon of London, in a letter to the editor of the *Lancet*, outlined a case report under the title "Calculus in the Bladder: Vesicovaginal Fistula: Advantages of the Gilt-Wire Suture." In January of that year he had operated on a woman who had suffered from a fistula for over 11 years and who had previously been unsuccessfully treated by Sir Astley Cooper. Three sutures were passed; one was removed at the end of 9 days; the second, at the end of 12 days; and the third was allowed to remain until 3 weeks had expired. The operation was a complete success. The sutures were made of gilded silver and Gosset stated that silver had the advantage of exciting little irritation and did not introduce ulceration with the same rapidity as silk or any other material. Apparently Gosset had used these sutures with uniform advantage for various conditions other than vesicovaginal fistula, and the article appears to indicate that the procedure was in use long before 1834.

In view of the foregoing the credit for priority in the use of the silver suture must go to Mr. Montague Gosset and not to J. Marion Sims. This should not detract from the remarkable work of Sims in the cure of vesicovaginal fistula as it is quite possible that he was not familiar with the previous work done in London when he proposed the silver wire suture in the treatment of this condition. The success of his operation as he gave it to the profession was dependent upon the Sims position, the Sims speculum, the special surgical

From the Department of Obstetrics and Gynecology and the Department of Urology, Carney Hospital.

needle, the indwelling catheter which he had invented, and the silver wire sutures. It was his well planned operation which resulted in the systematic treatment and cure of vesicovaginal fistula.

Originally, most vesicovaginal fistulas were due to the trauma of labor, frequently by the pinching of the bladder between the symphysis pubis and the presenting part during a long labor, with resulting pressure necrosis and sloughing of the bladder wall. In the majority of these cases the labor was terminated with forceps and the injury was ascribed commonly to the use of these instruments. Since the pressure necrosis had generally occurred before the application of the forceps, which were always used late in labor, it was in reality the withholding of the forceps rather than their employment that was responsible for the disaster. Simple obstetrical fistulas, excluding those that were adherent to one or the other pubic ramus and those in which there was great loss of tissue, could be closed usually through the vagina without too great difficulty. Three principles governed the success of these operations: first, satisfactory exposure through proper distention and exploration of the vagina; second, a suture which would not excite inflammation or ulceration; and third, a method of keeping the bladder empty during the process of healing. Obstetrical fistulas have become less common on account of the marked improvement in obstetric practice during the last half century.

Surgical fistulas have increased in number with the constantly increasing number of operations on the female pelvic organs. They may be due to direct bladder injury in operations for the repair of cystocele or for the vaginal or abdominal removal of the uterus. They may result also from necrosis following interference with the bladder blood supply. When a fistula is caused by direct operative injury, urinary leakage will be observed immediately after operation, but may not be noticed until later when due to necrosis and sloughing. The surgical fistulas frequently situated in a scarred vaginal vault high in the pelvis may be extremely difficult to expose and their closure, in many instances, presents a problem which will tax the ingenuity of the operator.

While the majority of vesicovaginal fistulas encountered are etiologically obstetrical or surgical, it must be remembered that there are other causes and of these the most common are carcinoma and irradiation. Syphilis and tuberculosis may be borne in mind and the continuous pressure of a foreign body, such as a pessary, may account for an occasional case.

PREOPERATIVE STUDY AND PREPARATION OF THE PATIENT

A few small fistulas close spontaneously, but the treatment of vesicovaginal fistula is surgical in most cases. In the authors' clinic it is regarded as a combined gynecological and urological problem. The initial studies in the hospital are made in the urological department. Cystoscopic examination determines the size and position of the fistulous opening in the bladder and especially its location with reference to the ureters and to the urethra. This is of the greatest importance in deciding upon the type of operation to be performed and in the avoidance of ureteral and sphincter injury at the time of operation. In cases of large fistulas, it is often necessary to place the patient in Trendelenburg position and to pack the vagina lightly with gauze in order to delay the vaginal escape of fluid enough to permit bladder distention and visualization of the bladder cavity. The lack of staining of this gauze, after dye has been placed in the bladder, will help to confirm the absence of a fistula at this level in difficult cases, while the appearance of color in the vagina, after indigocarmine intravenously, suggests a ureterovaginal fistula if vesical and urethral defects do not exist.

The urine is always cultured and the state of the tissues is carefully observed within the bladder and within the vagina in the region of the fistulous tract. A successful plastic operation cannot be hoped for in the presence of active infection and devitalized tissues cannot be expected to heal. A very important part of the preparation of the patient lies in the control or elimination of urinary tract infection. Appropriate antiseptic measures based upon the culture are carried out in all cases. Local irrigations of the bladder are not often necessary since the advent of chemotherapy and the antibiotics, but stones and incrustations upon

ulcerated surfaces need, of course, to be removed. If marked inflammatory changes are present around the fistula or in the skin externally, operation should be postponed until the structures involved have been restored to a state as nearly normal as possible and with no evidence of active infection. As a part of the preoperative study the condition of the upper urinary tract is investigated always by intravenous pyelograms or ureter catheterization, or both. In cases of active bladder infection, the latter may be withheld until the acute infectious process has subsided. It is important to determine the patency of the ureters and to learn whether or not they are dilated, and it is essential to know in advance of the operation the condition of the kidneys and their functional value. One of our patients had congenital polycystic disease. Two of our patients with vesicovaginal fistula had also a ureterovaginal fistula. In our experience, the communication between the ureter and the vagina is always associated with complete ureteral stricture below this level and usually is accompanied by some dilatation and infection in the ureter and kidney above.

In some cases of vesicovaginal fistula, in which there is danger of ureteral injury during the plastic repair, it is wise to place catheters within the ureters at the start of the operation. In certain difficult cases we have catheterized the fistula itself as an aid in the dissection. We have occasionally encountered a small fistula in the posterior lip of the internal sphincter margin or in the urethra just beyond, that could not be found until a ureteral catheter was passed upward through the opening in the vagina below.

SUTURE MATERIAL

In 1834 Montague Gosset of London successfully closed a vesicovaginal fistula with gilded silver wire sutures. In 1849 J. Marion Sims closed Anarcha's vesicovaginal fistula with silver wire sutures, at the thirtieth operation, having failed twenty-nine times with all the suture material he had previously utilized. The great advantages of silver wire are that it causes no inflammatory reaction in the tissues and that it is said to repel infection. The disadvantages are that it has low tensile strength, it cannot be tied, it must be fixed by twisting, and it may produce a disfiguring local argyria. In recent times a metal, rustless alloy steel wire, has come into use. Primarily recommended by W. Wayne Babcock of Philadelphia for the suturing of septic wounds, and recommended by him in the closure of vesicovaginal fistulas, this alloy wire has all the advantages of silver wire and none of its drawbacks. It is soft, strong, nonirritating and does not discolor the tissues. The tensile strength is such that a very fine gauge suture may be used and a strong knot may readily be tied. A century ago when vesicovaginal fistulas were first closed, there was but one operative technique, which consisted of paring the edges of the fistula and approximating them in one layer with sutures. It is obvious that metallic sutures, by their strength and lack of irritation, offered great advantages in that type of operation. With the development of surgical technique in general and of the operation for vesicovaginal fistula in particular, certain striking changes have occurred. Nowadays in the closure of difficult fistulas the bladder and the vagina are separated from each other and each structure is freely mobilized. Because of this dissection, the edges of the bladder and the vagina may be brought together without tension by fine suture material; fine chromic catgut can be used successfully in this type of operation while the larger strands of catgut failed in the classical Sims procedure. A method that has frequently proved advantageous in our hands consists of closing the bladder with fine chromic catgut sutures, avoiding the mucosa, and of closing the vaginal wall with alloy wire or silver wire sutures. In our opinion, silk and cotton have no place in the management of these fistulas. When working through the vagina in closing a vesicovaginal fistula in layers it is important not to resect the edges of the vaginal wall before approximating them, so as to avoid all tension, and to have sufficient vaginal wall with which to work should a recurrence develop requiring still another operation.

VARIETY OF OPERATIONS

On account of the great variety of vesicovaginal fistulas met in clinical practice, nu-

merous methods of closure have had to be devised. These may be summarized as follows:

1. The vaginal procedure, including several varieties of technique.

A. Paring the edges and closing them in one layer with silver wire or alloy wire sutures.

B. Circumcising the fistulous opening, turning a cuff into the bladder, closing the fistula by approximating the bladder musculature over the cuff without penetrating the bladder mucosa, and closing the vaginal wall separately. The vaginal wall may be satisfactorily closed by means of metallic sutures placed perpendicularly to the line of bladder suture, thus staggering the suture lines.

C. Mobilizing the bladder and closing the bladder and vagina in separate layers.

D. Using the cervix and body of the uterus to close the opening.

E. Suturing pedicled flaps from the vagina and vulva to bridge over the defect.

F. Using the gracilis muscle as a pedicle flap (Garlock technique.)

G. Colpocleisis.

H. Partial colpocleisis—Latzko.

2. The intravesical procedure through a suprapubic incision (Phaneuf and Graves) described and illustrated herein.

3. The suprapubic extraperitoneal procedure through a Pfannenstiel incision.

4. The intraperitoneal procedure through an abdominal incision (Legueu technique).

5. Implantation of ureters in the sigmoid.

THE INTRAVESICAL CLOSURE OF VESICOVAGINAL FISTULA

It is a well known fact that almost all vesicovaginal fistulas may be closed by the vaginal approach. There are, however, a certain few vesicovaginal fistulas so situated that they cannot be seen or exposed through the vagina. It is for this small group of cases that we have devised a method of intravesical closure which we are describing and illustrating as follows.

Operative procedure. The Trendelenburg position is used. A midline suprapubic incision, beginning low over the symphysis, exposes the extraperitoneal region of the bladder by separating the rectus muscles. Careful dissection of these muscles serves as a useful guide in approaching this region when normal cleavage planes have been obliterated by the scar of a previous operation. Separation of the recti from their sheaths on each side along the line of incision also adds to the ease of retraction. The fat and fascia overlying the bladder are divided beneath the symphysis and the anterior peritoneal reflection is dissected gently upward to expose in its entirety the anterior vesical wall. The sides of the bladder are then separated from adjacent fat or scar, as far downward as the region of the bladder neck. This free mobilization is very important and makes it possible to obtain a very satisfactory intravesical exposure of the area occupied by the fistula.

The bladder is opened in the anterior midline by an incision long enough and low enough to permit an adequate view of its cavity when a self-retaining retractor has been placed in position. A curved ribbon or tongue-depressor retractor held against moist gauze in the dome of the bladder helps to draw the region of the trigone and the fistula upward into the field. Ureteral catheters, usually of size 5 or 6 French, are now passed through the ureteral orifices to define the position of the ureters accurately during the operation. The internal orifice of the urethra is carefully observed and it also must be protected against injury. Silk traction sutures are placed in the bladder around the fistula, as shown by the artist, about 0.5 centimeter from the edge of the opening. These sutures, held upward, one at a time by the operator or his assistant, help greatly in the subsequent dissection.

The margin of the fistula is incised around its circumference with a small No. 15 Bard Parker blade and the whole thickness of the bladder wall is carefully separated from the vagina in all directions. The separation is carried out widely enough to permit the final repair of these structures without tension. Care must be used to avoid the ureters and further vaginal injury. In one difficult case, in which the fistula lay close to the outlet of the bladder, the operator placed fingers of the left hand in the vagina to guide the dissection, which in this region must preserve the urethral musculature. When bladder and vagina have been well mobilized, the vaginal opening is closed with interrupted sutures of No. 0 or No. 00

chromic catgut, depending upon the amount of scar tissue present. Great care is used in placing this first layer of sutures, which must accomplish complete approximation without tension. The defect in the bladder is now closed in one or two layers. When the thickness of its wall is adequate, the muscle alone is brought together with interrupted sutures of No. 00 chromic catgut, after which the mucosa may be approximated with a continuous suture of double zero or triple zero chromic catgut. The bladder and vaginal suture lines may be planned when possible to lie in opposite directions, but the bladder must be repaired always in a way that will result in a minimum of ureteral and urethral disturbance.

When the plastic procedure has been completed, the ureteral catheters are removed and the bladder is closed anteriorly with continuous fine plain catgut in two layers, leaving a mushroom catheter, size 26 French, in the upper pole of the incision for constant suprapubic drainage of urine. The catheter is irrigated gently with normal saline to be sure that it functions well. A small rubber tissue drain is placed on each side of the bladder to emerge through the prevesical space at the lower angle of the wound. The rectus muscles are approximated above and especially below the suprapubic catheter with interrupted sutures of fine plain catgut. The rectus fascia is closed with interrupted zero chromic catgut. Silk stay sutures may be used if desired. A suprapubic sinus thus formed will heal promptly when the drainage tube is removed. The stubborn sinuses are those which have been placed low in the bladder and just above the symphysis. The catheter should lie high in the wound and high in the bladder, where it will produce no irritation near the plastic repair.

Sterile constant urinary drainage is maintained with meticulous care. Bladder distention must be avoided, but irrigations are not used unless necessary. The best insurance against obstruction is a high fluid intake. Penicillin and sulfadiazine are given to combat infection. The drains in the prevesical space are removed usually in 4 or 5 days. The suprapubic catheter is taken out in 3 or 4 weeks, and in most cases the patient is kept in bed during all of that time.

SUPRAPUBIC BLADDER DRAINAGE IN VESICOVAGINAL FISTULA

Drainage of the bladder through a suprapubic incision is a common urological procedure, but a review of the chapter on vesicovaginal fistula in most of the important textbooks of gynecology fails to show any mention of this method of diverting the urinary stream after operations for vesicovaginal fistula. Suprapubic drainage has been described as a part of the intravesical operation that we have presented. We wish to emphasize its advantage also in difficult cases of vaginal repair. We use it frequently and regard it as one of the most important advances that we have made in the management of this problem. Diversion of the urinary stream is of obvious benefit during the process of healing and the suprapubic tube affords more certain drainage than the urethral catheter. Properly placed, it will remain in position; it is less likely to become obstructed and it will not produce irritation in the region of repair. It is especially important in those cases in which the fistula involves the urethra. Suprapubic drainage adds but little to the difficulty and shock of the operation. It is established immediately following the vaginal procedure in many instances in our clinic. Healing seems more certain; the care of the perineum is more satisfactory; and a well constructed suprapubic sinus never fails to close promptly in the presence of a normal bladder outlet. In the 40 cases of vesicovaginal fistula reported, 13 patients, 32.5 per cent, had suprapubic drainage, 4 after the intravesical operation and 9 after the vaginal procedure. We are convinced from our experience that the more common use of this method of drainage would lead to happier results in the management of difficult urinary fistulas.

SCHUCHARDT INCISION

Schuchardt's incision, also known as the paravaginal incision, was proposed in order to facilitate, through better exposure, the radical vaginal operation for carcinoma of the cervix. It is also of great value in exposing a vesicovaginal fistula situated high in the vagina, especially that which follows a panhysterectomy and which is situated in a scarred retracted vaginal vault. It is usually performed on the

left side, and the length of the incision is governed by the amount of room required. We have found this procedure to be extremely valuable. It was used in 11 of the 40 cases included in this study, or in 27.5 per cent.

POSTOPERATIVE CARE

Regardless of the type of operation employed in cases of vesicovaginal fistula, the postoperative care is of vital importance. It requires close supervision, preferably by the operator himself, and it never should be delegated to inexperienced assistants. The primary consideration is the avoidance of bladder distention and infection during the period of healing. Every precaution must be taken to prevent interruption of catheter drainage. The suprapubic or urethral catheter must be maintained unobstructed and in good position. As has been stated, we prefer suprapubic drainage in the difficult cases. Irrigations, always gentle and without bladder distention, are used as little as possible to minimize the risk of the introduction of fresh infection. Vigorous antiseptic solutions, productive of irritation or discomfort, are unnecessary. Potassium permanganate solution is used most often in our cases. The best and safest irrigation is provided by an adequate fluid intake. It is not necessary to irrigate a catheter that is freely discharging clear urine. Until the patient is able to take by mouth and retain an average of 2500 to 3000 cubic centimeters of liquids each day, parenteral fluids are essential. These will vary in amount and kind with the general state of the patient and her circulatory condition.

Infection in the bladder and vagina is always reduced to the minimum before surgery is undertaken in these cases. Bacteriological study of the urine is made at the time of the original examination and as often as indicated during the convalescence. The antiseptic program is based upon these cultures. Sulfadiazine is given usually a few days before operation, 0.5 gram every 4 hours day and night, combined with sodium bicarbonate 1.0 gram, and continued for several days after operation. When it is apparent that infection is well controlled, these medicines may be given at 6 hour intervals and we omit them entirely in most cases within 7 to 10 days after surgery to avoid occlusion of the catheter with alkaline deposits. For the remainder of the convalescence the patient receives methenamine and sodium biphosphate, 15 grains of each 4 times daily. Indwelling catheters become obstructed less quickly when the urine is acid. Penicillin is used as a rule for the first few days after operation until the temperature is normal and the wound is healing well. We resort to streptomycin whenever necessary; it is important to remember that this drug has been shown to be more effective in an alkaline urine.

Urethral catheters are removed as a rule in about 14 days. Suprapubic catheters are allowed to remain for 3 to 4 weeks. When metallic sutures have been resorted to in closing the vagina, they are removed at the end of 4 weeks, always under anesthesia. Intravenous anesthesia serves a useful purpose in this connection, but general anesthesia may be employed if preferred. The patient is permitted to get out of bed the day after the drainage apparatus is removed. When urethral drainage is employed, she may be allowed to go home on the 15th postoperative day, to return to the hospital in 2 weeks, or in 1 month from the time of the operation to have the metallic sutures removed, if wire has been used.

URETEROINTESTINAL ANASTOMOSIS FOR IRREPARABLE FISTULAS

An occasional case of vesicovaginal fistula is encountered in which there seems to be little likelihood of achieving urinary control by any of the described procedures. In such cases it is desirable, in some instances, to resort to transplantation of the ureters to the large bowel. The most common reasons for this operation are: first, destruction of the bladder sphincter which will render the patient still incontinent, even though the fistula be repaired, and second, necrosis leading to fistula as a result of irradiation. Ischemia, produced by radium or x-ray with endarteritis and fibrosis around the periphery of a fistula, does not present a favorable field for plastic surgery.

There have been 6 patients in this series who have had ureterointestinal anastomoses. Two had urethrovaginal fistulas with severe urethral injury and loss of the sphincter mus-

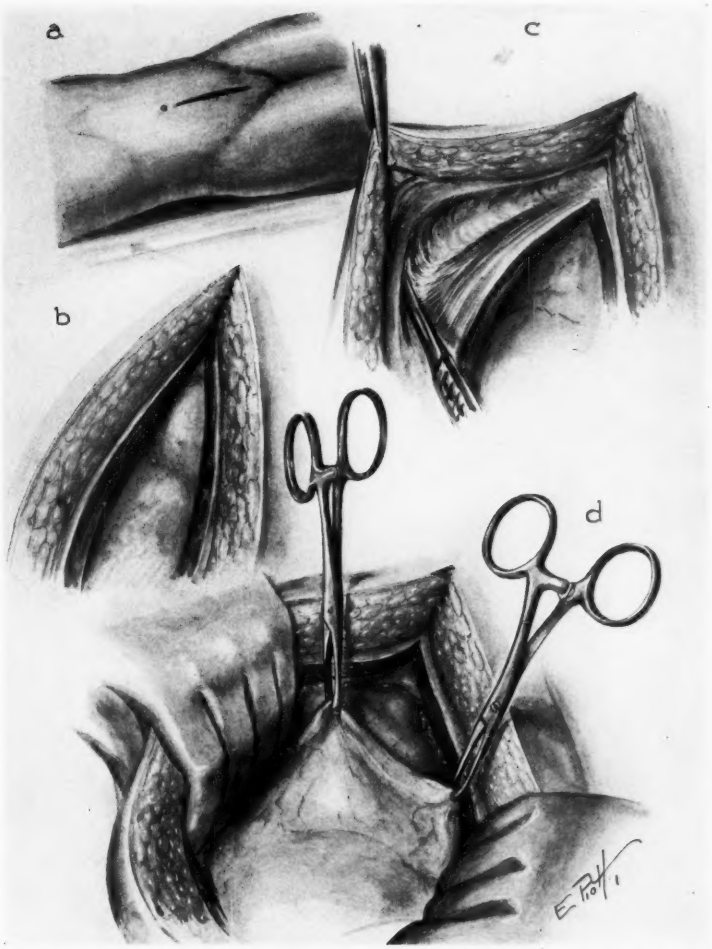

Fig. 1. Artist's drawing. a, Median suprapubic incision between the symphysis and the umbilicus. b, The incision is carried down to the fat overlying the peritoneum and the anterior bladder wall. c, The medial portion of the rectus muscle on each side is exposed and freed anteriorly and posteriorly down to the symphysis to permit wide retraction. d, The bladder wall is grasped with Allis clamps after dividing the fatty layer which covers it. The anterior peritoneal reflection is dissected upwards.

culature. Two had very complicated problems that were seen before the development of the suprapubic operation that we have described. Another patient had an irradiation fistula following the treatment of carcinoma of the cervix. Still another had tuberculosis in the bladder and but one functioning kidney. The clinical result has been gratifying in all of these cases. Their records are abstracted briefly:

Mrs. D.B., aged 46 years, Carney Hospital No. 361467, was admitted May 28, 1936. There was a history of vesicovaginal fistula following hysterectomy for fibroids. A second operation had been attempted to close the fistula and, at this time, a strictured right ureter was tied. Suprapubic operation was performed by us June 9, 1936. The right half of the bladder was removed. Pathological report was: tuberculosis. Incontinence persisted.

Left nephrostomy on December 9, 1937, was carried out to afford preliminary drainage and to reduce

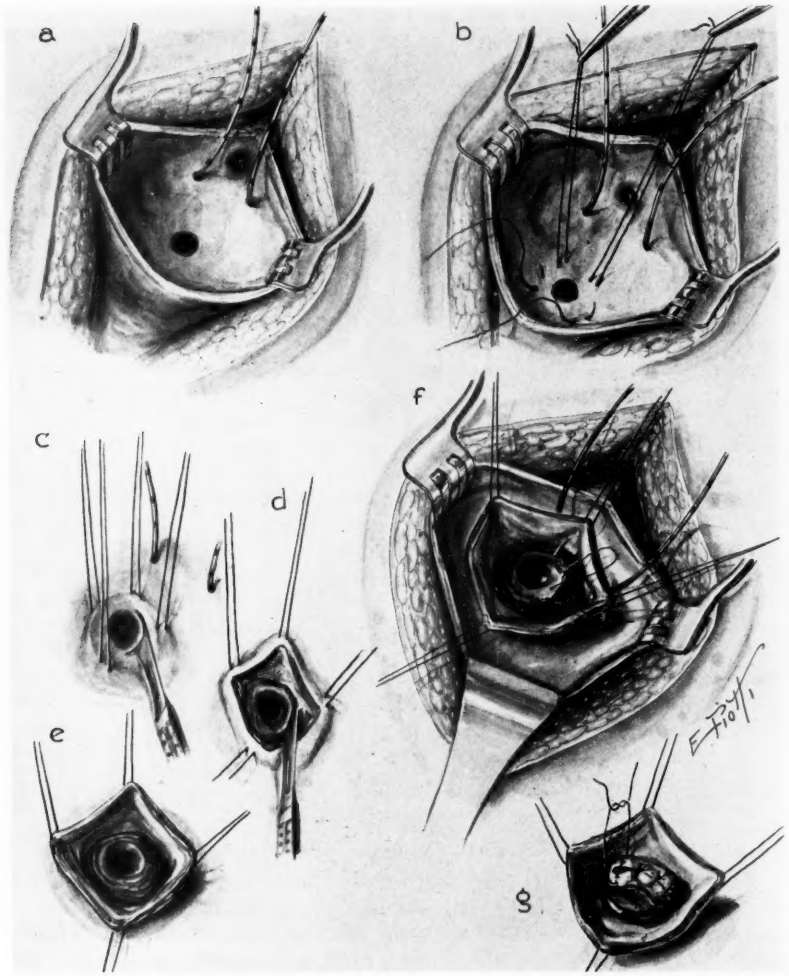

Fig. 2. Artist's drawing. a, The bladder has been opened in the mid-line and a self-retaining retractor has been introduced. The urethral orifice is seen and ureteral catheters have been passed. The fistula is exposed but the artist has placed it higher than the usual position. b, Four traction sutures of fine black silk are introduced. c, The dissection is begun by incising the margin of the fistulous opening. d, The bladder wall is carefully separated from the vagina with a fine scalpel. e, The dissection is completed. There is free mobilization of the bladder and vagina. f, The vaginal opening is closed with interrupted sutures of No. 0 or 00 chromic catgut. g, The vaginal portion of the fistula is closed.

the risk of ureteral transplantation in the case of a single kidney. Left ureterointestinal anastomosis was performed on January 15, 1938. The result was satisfactory. The patient had a spinal fusion operation for tuberculosis in December, 1941, with no untoward complications. She was last seen on December 16, 1947, almost 10 years after ureterointestinal anastomosis at age 58 years. She reported a good appetite. Her weight had remained the same for several years. She was drinking about 3 quarts of liquids every day, and said that there had been no diminution in her rectal output. The intervals between voidings were sometimes 2 to 3 hours by day; nocturia once. She looked very well. Her color was

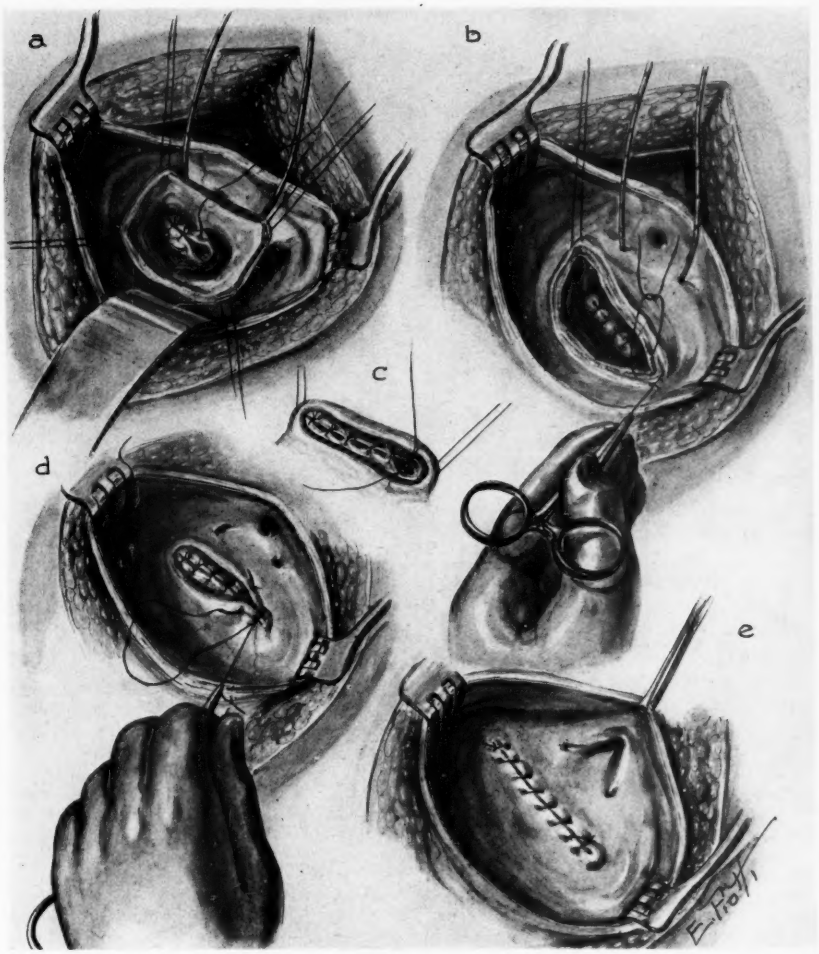

Fig. 3. Artist's drawing. a, A second layer of interrupted sutures of No. 00 chromic catgut is applied in the vaginal wall when possible. Because of tension this layer has to be omitted in some cases. b, The closure of the bladder is begun with interrupted sutures of No. 00 chromic catgut in the bladder musculature, avoiding the mucosa. c, The closure of the muscular layer is completed. d, The bladder mucosa is closed with a running suture of No. 00 or 000 chromic catgut. e, The vesicovaginal fistula is now closed. The urethral and ureteral orifices are uninjured.

good. Blood pressure 155/75. The abdomen was not remarkable except for weakness of its wall in the regions of the scars. Fasting nonprotein nitrogen was 62 milligrams. The nonprotein nitrogen was 57 milligrams in April, 1944. Intravenous pyelograms showed faint excretion of dye by the left kidney in 25 minutes, with evidence also of some dye in the sigmoid. This appears to have been a satisfactory clinical result in a difficult problem, in spite of present signs of impaired renal function.

Mrs. G. H., aged 40 years, Carney Hospital No. 381817, was admitted June 15, 1938. History of panhysterectomy for pelvic inflammatory disease followed by a vesicovaginal fistula and two unsuccessful repair operations. At examination a large fistula was found close to the ureters and heavily incrusted with urinary salts. A suprapubic cystostomy was performed first to prepare the bladder and vagina for subsequent plastic surgery. Ureterointestinal anastomosis was refused. Colpocleisis was

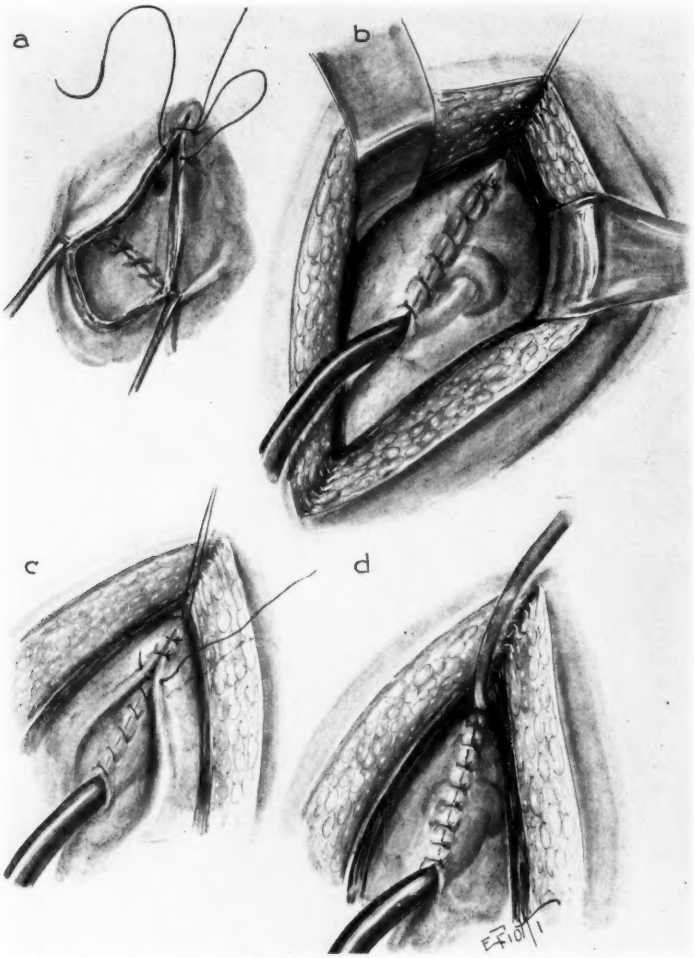

Fig. 4. Artist's drawing. a, The anterior bladder wall is closed in two layers with running extra mucosal sutures of No. 0 plain catgut. b, A mushroom catheter, size about 26 French, drains the bladder at the apex of the incision. c, and d, The wound is closed. Small rubber tissue wicks drain each side of the bladder and the prevesical space at the lower angle of the wound. The rectus muscles are approximated above and below the catheter with interrupted sutures of fine plain catgut. The rectus fascia is closed with interrupted sutures of No. 0 chromic catgut.

done by Dr. Phaneuf on August 23, 1938 and secondary closure of small point of urinary leakage on October 14, 1938. Patient was discharged November 13, 1938, voiding normally, incontinence relieved.

She returned to the hospital in 1939 because of domestic difficulties arising from the interruption of normal marital relations. Left ureterointestinal anastomosis was performed on November 7, right ureterointestinal anastomosis on February 5, 1940, vaginal plastic operation to reopen the vagina, by Dr. Phaneuf, March 12, 1940. Patient was last seen in the office on November 24, 1942. She had been perfectly well. Complete examination was not possible because she was leaving for California the next day. She looked well, had good color, and a clean, moist tongue. The abdomen was essentially normal. Intravenous pyelograms in July, 1944, showed excretion of the dye by both kidneys in 5 minutes.

There was moderate dilatation on the right side. The clinical result seemed satisfactory.

Mrs. B.C., aged 37 years, Carney Hospital No. 394470, was admitted December 2, 1939. There was a history of panhysterectomy in August, 1939, followed by vaginal fistula. After an attempt to close this in October, 1939, the patient had developed an enterovaginal fistula. Carney Hospital diagnosis after urological study was: fistulas—vesicovaginal, enterovaginal, and ureterovaginal, left. Closure of enterovaginal fistula was carried out by Dr. Phaneuf on December 13, 1939. The fistulous tract was found to lie between the vaginal cuff and an adherent loop of ileum.

Right ureterointestinal anastomosis was done on March 28, 1940, left ureterointestinal anastomosis on July 30, 1940. Patient was last seen in September, 1947, over 7 years after the ureteral transplantations. Her general condition was excellent. Fasting nonprotein nitrogen was 40 milligrams. Intravenous pyelograms showed excellent excretion of the dye by both kidneys in 5 minutes. There was slight dilatation on the left side. The clinical result seemed very satisfactory.

Mrs. E.B., aged 35 years, Carney Hospital No. 381424 was first seen in January, 1938, when a urethrovaginal fistula followed operation for the removal of a large infected cyst or diverticulum of the urethra. Immediate repair was attempted without success. Suprapubic cystostomy and plastic operation upon the outlet of the bladder was done in November, 1938. Incontinence persisted. Patient continued to wear suprapubic tube. Plastic reconstruction of urethra was carried out in June, 1941, without success. Hysterectomy was performed by Dr. Phaneuf for fibroids and endometriosis and chronic salpingo-oophoritis in July, 1942.

Left ureterointestinal anastomosis was performed on September 16, 1943, right ureterointestinal anastomosis on July 17, 1944. Patient was last seen in July, 1947. Nonprotein nitrogen was 40 milligrams on July 10, and 28 milligrams on July 15. Blood pressure was 130/90. Intravenous pyelograms showed the dye to be excreted by both kidneys in 5 minutes. There was slight dilatation of the renal pelvis and ureter on each side (Fig. 5). The clinical result seemed satisfactory.

Mrs. A.S., aged 52 years, Carney Hospital No. 446056, was admitted November 30, 1944. There was a history of cauterization of a urethral caruncle in 1939. This was repeated in 4 months and incontinence followed. There had been 4 unsuccessful attempts to repair the urethra between 1940 and 1943. Examination at the Carney Hospital revealed the urinary meatus lined with slough. The anterior vaginal wall was intact but scarred. Urethral destruction considered too complete for further plastic surgery.

Right ureterointestinal anastomosis was performed on September 22, 1944, left ureterointestinal anastomosis on May 1, 1945. Patient was last seen in October, 1947. Nonprotein nitrogen was 42 milligrams on October 6, and 32 milligrams on October 10. Intravenous pyelograms showed the dye to be excreted by each kidney in 5 minutes. There was slight dilatation on the right side. The clinical result seemed very satisfactory (Figs. 6, 7, 8, and 9).

Fig. 5. Intravenous pyelogram in case of Mrs. E. B., Carney Hospital No. 381424, three years after ureterointestinal anastomosis.

Mrs. B.E., aged 65 years, Carney Hospital No. 464687, was admitted September 9, 1946. There was a history of large vesicovaginal fistula beginning in September, 1944, following a program of x-ray therapy and radium completed in August, 1943, for the treatment of epidermoid carcinoma of the cervix, grade 3. There had been one unsuccessful attempt to close the fistula by a vaginal operation combined with suprapubic drainage. Examination by the authors disclosed no evidence of persistent malignant disease. The vagina was 2 to 3 centimeters in length. The urethra was absent except for its distal third. Cystoscopy found the region of the trigone to be replaced by an area of slough and necrosis.

Exploratory laparotomy to exclude persistent cancer and right ureterointestinal anastomosis was performed on September 23, 1946, left ureterointestinal anastomosis on October 17, 1946. The immediate result was very satisfactory. A letter received from the family physician in July, 1947, stated: "Her general condition is excellent. Except for the times when she is nervous and upset, her control is excellent." The blood pressure was 140/86. The nonprotein nitrogen was 29. The intravenous pyelograms showed no evidence of either hydronephrosis or hydroureter.

The whole problem of ureterointestinal anastomosis and the technique employed at the

SUMMARY OF METHODS USED IN CLOSING THESE 40 FISTULAS

	No. cases
Sims' classical operation (Cases 1, 2, 3, 12, 15)	5
Suprapubic extraperitoneal closure. Later, vesical implantation or right ureter (Case 5)	1
Vaginal flap method* (Cases 4†, 6, 7, 8, 9, 10, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 29, 32, 34)	20
Transplantation of ureters in sigmoid (Cases 11, 16, 37, 38, 39, 40)	6
Colpocleisis (Case 13)	1
Colpocleisis and later transplantation of ureters in sugmoid (Case 14)	1
Implantation of right ureter in bladder and suprapubic intravesical closure (Case 28)	1
Suprapubic intravesical closure (Cases 30, 35, 36)	3
Vaginal flap method. Reconstruction of urethra (Cases 31, 33)	2
Total	40

*The vaginal flap method consists of making a vaginal incision through or around the fistula, developing two vaginal flaps, mobilizing the bladder, closing the bladder opening with fine catgut and the vaginal incision with silver wire, alloy wire, or catgut.

†Case 4—Vaginal closure by another surgeon after 2 failures at the Carney Hospital.

Carney Hospital will be discussed in a later communication from the Urological Department.

RESULTS

There was no fatality in this series of 40 cases. The end-result in 39 cases showed the patient to be cured. The case of 1 patient is not completed. A short summary follows:

CASE 36. Mrs. B.T. had a large vesicovaginal fistula about 3 centimeters in diameter. This had occurred on March 9, 1938, as a result of the high forceps delivery of her third child, a large male child, who had died at birth. This delivery had been complicated by puerperal sepsis. The fistula which was situated high under the symphysis pubis could not be exposed for closure through the vagina. She also had a myomatous uterus the size of a 3 months' gestation. The patient was operated upon at the Carney Hospital on June 18, 1946, a panhysterectomy and double salpingo-oophorectomy being performed. She made a satisfactory recovery. On October 18, 1946, she had an intravesical closure of the fistula by the method which we have presented, under continuous spinal anesthesia. This was the most difficult operation for vesicovaginal fistula that we had thus far performed. She was discharged from the hospital on December 8, 1946, at which time she voided large amounts of urine, at one time on the previous day having passed 12 ounces, about 360 cubic centimeters of urine.

Examination at Dr. Phaneuf's office on January 2, 1947, showed the following: The abdominal incision was well healed. On the introduction of a Sims speculum a small amount of urine was found in the vagina. The vaginal scar which was hidden under the symphysis could not be seen, it was found to be perfectly smooth on palpation. On close observation, after some time, the escape of a minute quantity of urine was observed as it came from the right side of the scar. Thus, the fistula, which originally had been the size of a silver half dollar, had been converted into a pinpoint opening.

The patient has returned to her home in California. A letter received from Dr. Frank Hinman of San Francisco in June, 1947, stated that cystoscopy had revealed a small fistulous opening in the bladder, about 4 millimeters in diameter, in the superior portion of the scar on the right side. A functioning right ureter was not found. He felt hopeful that this remaining fistula could be closed successfully.

ABSTRACT OF CASES

The 5 case abstracts that follow are reported because of their unusual interest.

CASE 13. Mrs. A.S., an obese woman, 59 years of age, had had a supravaginal hysterectomy for fibroids in a neighboring state. Sometime thereafter she had bleeding from the cervical stump and operation, consisting of excision of the cervix through the vagina, was performed. The trigone of the bladder was removed with the cervix. When she was examined at the Carney Hospital she had a large vesicovaginal fistula which occupied the vaginal vault. The ureteral orifice on each side was caught in the scar and could be seen ejecting urine. On March 25, 1938, a colpocleisis was performed, alloy wire sutures being used. The convalescence was uneventful. On April 15, 1938, the alloy wire sutures were removed. Urinary continence had been established. On May 23, 1938 an examination showed the vagina to be 5 centimeters in depth. The patient had urinary control and was enjoying good health.

CASE 14. Mrs. G. H., 40 years of age, and reported previously as a case of ureterointestinal anastomosis, had been operated on elsewhere on July 20, 1937, the operation consisting of a panhysterectomy and double salpingo-oophorectomy for pelvic inflammatory disease. The bladder had been injured at the time of operation and a vesicovaginal fistula had appeared immediately. On September 1, 1937, she was operated on again by the same surgeon, an abdominal closure of the vesicovaginal fistula being attempted; this was unsuccessful. On December 28, 1937, a vaginal closure of the fistula was undertaken again without success. She was referred to one of us on April 28, 1938, when an examination was made. A lighted speculum, placed in the vagina revealed a large fistula at the apex of the vaginal vault. The opening was filled with a mass of urinary concretion. The vulva, the vagina, and the inner aspects of the thighs were markedly excoriated. Later, urological studies revealed that the left ureteral orifice was close to the margin of the fistula. Much scar tissue had

Fig. 6.

Fig. 7.

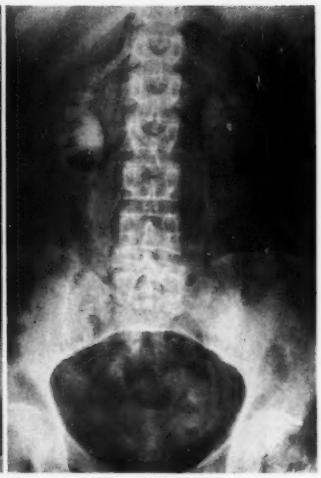

Fig. 8.

Fig. 6. Intravenous pyelogram before operation in case of Mrs. A.S., Carney Hospital No. 446056.

Fig. 7. Intravenous pyelogram in case of Mrs. A.S., Carney Hospital No. 446056, about 2½ years after ureterointestinal anastomosis, 5 minute film. Note the junction of ureter and bowel clearly shown on the left side.

Fig. 8. Intravenous pyelogram in case of Mrs. A.S., Carney Hospital No. 446056, about 2½ years after ureterointestinal anastomosis, 15 minute film. Note the junction of ureter and bowel clearly shown on the left side.

Fig. 9. Intravenous pyelogram in case of Mrs. A.S., Carney Hospital No. 446056, about 2½ years after ureterointestinal anastomosis. Note the dye outlining the distal portion of the large bowel.

formed subsequent to the two previous attempts at closure. The fistula was pulled upward under the symphysis and was inaccessible for closure through the vagina. The patient was given the choice of two methods, transplantation of the ureters into the sigmoid, or colpocleisis. It was explained to her that colpocleisis meant the cessation of marital relations. She was emphatic in stating that future marital relations meant nothing to her, and she chose the second of the two procedures.

On August 23, 1938, a colpocleisis was performed at the Carney Hospital. This healed except for a small area in the line of suture, which allowed the leakage of a small amount of urine externally. On October 24, 1938, this defect was closed successfully. She was now continent and voided through the urethra. Later, however, she became dissatisfied with the cessation of her normal marital life and she demanded that the vagina be reopened. On December 3, 1939, one ureter was implanted in the sigmoid while the second was similarly treated on February 5, 1940. On March 12, 1940, a vaginal plastic operation was performed to reopen the vagina. A large glass dilating plug was introduced in the vagina and was worn constantly. She was next seen in the office by one of us on April 11, 1940. The vaginal introitus and vagina admitted two fingers. The vesical fistula was readily felt and admitted the tips of the two examining fingers. The vagina was healthy in appearance; there was no irritation present and the operative results appeared to be satisfactory. Coitus had been indulged in. She was advised to discard the glass vaginal plug during the day but to wear it at night. On May 28, 1940, the vagina appeared to be roomy and she was advised to continue to wear the large glass plug at night and to continue with sexual congress. She failed to keep subsequent appointments, but returned to the office on Febru-

Fig. 9.

Fig. 10. Intravenous pyelogram in Case 28, Mrs. M.H. Healed vesicovaginal fistula, polycystic disease of the kidneys and ureterovesical transplantation on the right side.

ary 20, 1941. She had not worn the glass plug since August, 1940, the vagina was somewhat contracted at the junction of its middle and lower thirds, the introitus admitted two examining fingers. The narrowing was believed to be due to disuse. A medium-size glass plug was inserted and she was asked to return in one month for the introduction of a larger one. She was entirely satisfied with her urinary control. She was last seen on May 12, 1941, when the following note was made: "The vaginal introitus readily admits two fingers, the vaginal walls are soft and healthy in appearance, a medium bivalve vaginal speculum can be used without difficulty, the second to the largest glass vaginal plug can be introduced with some difficulty. Urinary control is satisfactory."

CASE 25. Mrs. C. O'C., 42 years of age, was operated on at the Carney Hospital for a vesicovaginal fistula on October 3, 1942. The fistula had developed after an instrumental delivery of her first child, 17 years previously. Three operations had been performed in another state in an attempt to close the fistula; the first operation was performed in 1938, this was not successful; the second operation was performed on August 11, 1941, and consisted of a vaginal hysterectomy and closure of the fistula which also resulted in failure; the third operation was performed on October 14, 1941, and consisted of vaginal closure of the fistula; this also resulted in failure. At the time of her admission to the Carney Hospital, the vagina contained a considerable amount of sloughing tissue, and the vagina, the vulva, and the inner aspect of the thighs were covered with deposits of urinary salts. Careful preliminary measures were necessary to prepare these areas for surgery. The operation which was performed on October 3, 1942, consisted of a left Schuchardt incision and the vaginal closure of the fistula after free mobilization, with interrupted sutures of No. 0 chromic catgut placed in the bladder wall in a transverse direction. This completely closed the bladder opening. Next a flap of musculofascial tissue was split from the left vaginal wall flap and sutured over the region of bladder repair by means of interrupted sutures of No. 0 chromic catgut. This reinforced the bladder suture line. Finally the vaginal mucosa was closed with five interrupted sutures of steel alloy wire. The Schuchardt incision was repaired and a suprapubic cystostomy was performed. The convalescence was uneventful. The suprapubic catheter was removed on October 24, 1942, and the suprapubic sinus had healed completely on October 28, 1942. The alloy wire sutures were removed on October 28, 1942. There was no sign of a fistula and the patient was allowed out of bed on that day. She was examined in the office on December 9, 1942, July 15, 1943, and May 31, 1944, all examinations showing a well healed fistula and urinary continence.

CASE 28. Mrs. M. H., 38 years of age, had had a panhysterectomy and double salpingo-oophorectomy for uterine myomas on April 4, 1944. Shortly after operation a large vesicovaginal fistula was found and the patient appeared to be completely anuric. A urologist was called in consultation. In addition to the large vesicovaginal fistula, he discovered occlusion of both ureters at the bladder level. He performed bilateral nephrostomies on April 6, 1944, and at this time learned that the patient had congenital polycystic disease of the kidneys. When urine later began to flow from the vagina through the fistulous opening, the nephrostomy sinuses were allowed to close. Subsequently the surgeon who had done the hysterectomy performed two vaginal operations for closure of the fistula, neither of these being successful. She was referred to one of us, L. E. P., and sent to the Carney Hospital for complete urological studies. It was found at this time that the left ureter was patent, and that the right ureter was strictured about 4 centimeters above its entrance into the bladder. A right ureteral fistula had occurred above the stricture and this fistula was in contact with the large vesicovaginal opening, permitting the escape of urine from the right kidney. The first step in our course of treatment was the implantation of the right ureter in the posterosuperior portion of the bladder. Healing was satisfactory and the function of the right ureter was demonstrated by urograms. The next step was an attempt to close the vesicovaginal fistula through the vagina on December 14, 1944. The orifice of the left ureter was close to the left side of the fistula; for this reason a ureteral catheter was passed on that side to lessen the likelihood of ureteral injury during the operation. A wide left-sided Schuchardt incision was made. The fistula was hard to expose as there was extensive scar tissue resulting from the first two attempts at closure, and the right

end of the fistulous opening was pulled upward and behind the right pubic ramus. It was impossible to separate the vagina from the bladder under these conditions. Therefore, the edges of the fistula were pared according to the Sims technique, and the opening was closed with six interrupted sutures of No. 30 steel alloy wire. The Schuchardt incision was closed and suprapubic drainage was established. The catheter in the left ureter was left *in situ* for a few days. On January 16, 1945, the six steel alloy wire sutures were removed. There was still a slight escape of urine into the vagina, on the right side. The patient was examined at the office on March 7, 1945; there was persistent urinary leakage from the vesicovaginal fistula.

On May 21, 1945, intravesical closure of the fistula was carried out by the authors, under continuous spinal anesthesia, by the technique described. The patient never passed any urine through the vagina from that time on. Healing took place by first intention. She was allowed to void on the twenty-first day. She was discharged from the hospital on June 21, 1945, the fistula being closed and both kidneys draining into the bladder. Intravenous pyelograms in July 1945 showed fair renal function on each side with good concentration of the dye in the 25 minute film (Fig. 10). Changes in the kidney pelves due to polycystic disease are seen. The right ureter, which has been transplanted to the dome of the bladder, is shown, with no significant dilatation. On August 18, 1945, examination at the office revealed the vaginal vault to be smooth, the anterior vaginal wall to be well healed, the fistula to be closed, and the result satisfactory. At the last office visit, April 17, 1947, the patient looked very well and had no symptoms. A voided sample of urine showed no abnormalities microscopically. At abdominal examination both kidneys were found to be palpable and the right one smaller than the left. Blood pressure was 175/85.

SUMMARY AND CONCLUSIONS

1. The distressing condition of vesicovaginal fistula originally was due to obstetric causes. The majority of urinary fistulas seen today follow operations on the female pelvic organs. The latter are the more difficult to repair because of their inaccessibility and the firm scar tissue which surrounds them.

2. The first operation on record for the closure of vesicovaginal fistula is that of Mr. Montague Gosset of London, in January, 1834; he had used gilded silver wire sutures. George Hayward of Boston reported a successful operation in 1839 as well as two others in 1851.

3. J. Marion Sims closed his first vesicovaginal fistula in May, 1849, having operated on the slave girl, Anarcha, for the thirtieth time, and having used silver wire sutures for the first time. It is very probable that Sims knew nothing of the work done in London when he proposed the silver wire suture.

4. The various procedures used in closing vesicovaginal fistulas are tabulated.

5. We are of the opinion that most vesicovaginal fistulas can be closed by the vaginal route.

6. For the few cases in which the fistula cannot be exposed through the vagina, we describe and illustrate an intravesical operation which has given us excellent results.

7. In 6 cases in this series, for reasons that have been presented, ureterointestinal anastomoses were performed, with satisfactory results.

8. The advantage of suprapubic drainage in the management of difficult vesicovaginal fistulas is emphasized.

9. The preoperative and postoperative care, as well as the suture material, are discussed.

10. Thirty-four cases (plus Dr. Graves' 6 cases of ureterointestinal anastomosis) with their end-results are reported.

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MICROPLETHYSMOGRAPHY AS A CRITERION FOR SYMPATHECTOMY IN HYPERTENSION

RAYMOND S. MEGIBOW, M.D., HAROLD NEUHOF, M.D., F.A.C.S.,
SERGEI FEITELBERG, M.D., New York, New York

ORGANIC vascular disease is considered to be the principal factor which limits the possible effectiveness of surgical operation on the sympathetic nervous system in the treatment of "essential" hypertension. For this reason a number of test procedures have been developed in order to select those patients in whom an elevated blood pressure is maintained by vasospasm rather than by organic vascular disease (1, 5). The value of the described methods is questionable because a significant statistical correlation between preoperative prognostication and postoperative result has not been established. Recently methods have been devised which, while capable of accurately forecasting surgical results (4, 6), are open to certain criticisms. The methods require hospitalization, they necessitate specialized techniques, and most important, they constitute surgical procedures with an attendant small but distinct morbidity if not mortality. It is apparent that the need for an objective, safe and simple test still exists. Ideally this should afford as well, accurate information as to the existence, extent, and severity of vascular changes.

Since December 1945, one of us (RSM) has been systematically analyzing the volume pulse changes of the fingers and toes in a variety of cardiovascular and allied diseases. During the early part of this period, special attention was paid to hypertensive patients who underwent operations. The initial observations were of sufficient interest to warrant their supplementation by more detailed investigations. These studies have resulted in the development of a procedure which promises to be of value in the identification of those hypertensive patients who are to benefit from sympathectomy.

From the Clinical Services and Department of Physics, The Mount Sinai Hospital.
Dr. Megibow, fellow in Medicine, Rosenstock Memorial Foundation.

METHODS

Continuous recordings of the volume fluctuations in both the finger and toe tips were obtained by means of a new ink writing photoelectric microplethysmograph constructed by one of us (S. F.). Variations less than 1 cubic millimeter are easily recorded through a pneumatic system. Sensitivity which may be varied up to full chart scale (50 divisions) for a volume change of 20 cubic millimeters, is usually adjusted to produce a deflection of 10 to 20 divisions. Calibration may be effected manually at any time or automatically every 10 minutes, by introducing a volume change of 20 cubic millimeters into the system. The response of the pen is linear within 5 per cent over the 50 divisions, and corrections for variations in linearity are computed by calibration over the entire scale. At a sensitivity of 1 division per 1 cubic millimeter the noise level is less than ¼ division corresponding to a volume change of less than 0.25 cubic millimeter. Four recording speeds are available depending upon the gear arrangement. The natural frequency is 5 cycles per second and the instrument is critically damped. The timing is automatic.

The precautions and methods for plethysmographic recording have been described previously (2). Plethysmograms were obtained in 118 hypertensive patients, 30 of whom ultimately underwent more or less radical abdominothoracic sympathectomy. The same technique was employed for all patients. It consisted of obtaining plethysmograms from both great toes and occasionally from the second and third fingers of both hands after attempted vasodilatation by pharmacological or by physical means. In all instances continuous recordings were made until the effects of vasodilatation could be accurately appraised. At least 2 separate control observations were made in those patients who subsequently were subjected to operation. They were then studied at

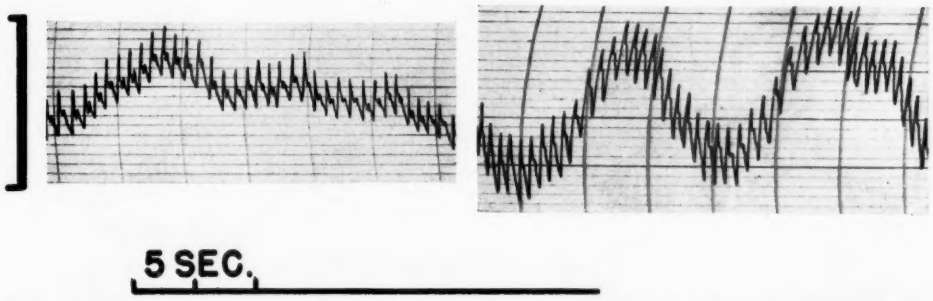

Fig. 1. Toetip plethysmograms; tracing from a normal subject on the left, and from a hypertensive subject on the right. Note the differences in both the position of the dicrotic notch and in the amplitude of the alpha waves in both records. (In these and in all subsequent tracings the calibration on the left represents a volume change amounting to 20 cubic millimeters. Spacing between the ordinates equals 5 seconds.)

intervals following both unilateral and bilateral sympathectomy.

The plethysmograms were calibrated frequently in order to insure accurate standards for measurement and comparison. The analysis of all the tracings was based on the contour of the volume pulse wave, the amplitude of the volume pulse, the amplitude of the alpha waves, the overall volume and the changes which followed attempted vasodilatation.

In most patients physical examination was supplemented by teleoroentgenograms, electrocardiograms, and intravenous pyelograms. Retinal changes were evaluated by ophthalmologists. Renal function was determined both by the excretion of diodrast as noted on the pyelogram and by the excretion of phenolsulfonphthalein. The blood pressure was measured sphygmomanometrically at frequent intervals. The changes in blood pressure which followed sodium amytal, were measured in all but 7 of the 30 patients who underwent operation.

RESULTS

Figure 1 illustrates the plethysmogram of both a normal and an untreated hypertensive patient. Although the volume pulses of both are characterized by a sharp peaked apex, by a distinct dicrotic notch and by a more vertical systolic than diastolic limb, it is to be noted that the dicrotic notch is inscribed nearer to the apex and, as a rule, the magnitude of the alpha deflections is greater in the hypertensive than in the normotensive subject. The proximity of the dicrotic notch to the apex of the volume pulse appears to be related to the height of the diastolic pressure since the dicrotic notch is in general found to be at a higher position on the diastolic limb in the presence of severe rather than of mild diastolic hypertension. However, since we have encountered considerable overlapping, too much prognostic significance has not been ascribed to volume pulse wave contour changes of this variety. On the other hand certain other alterations in the intrinsic digital volume fluctuations may be prognostically important, since on occasion, they may reflect the development of diseases which not infrequently complicate hypertension. Thus a decrease in the normal slope inequality of the systolic and diastolic limbs, a blurring or disappearance of the dicrotic notch, and a reduction in the amplitude or a complete disappearance of the alpha waves may represent coexist-

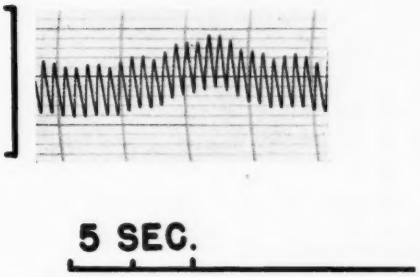

Fig. 2. Toetip plethysmogram in a patient with both hypertension and arteriosclerosis. Note the absence of the dicrotic notch, the inconspicuous alpha waves, and the loss in the normal slope inequality of the systolic and diastolic limbs.

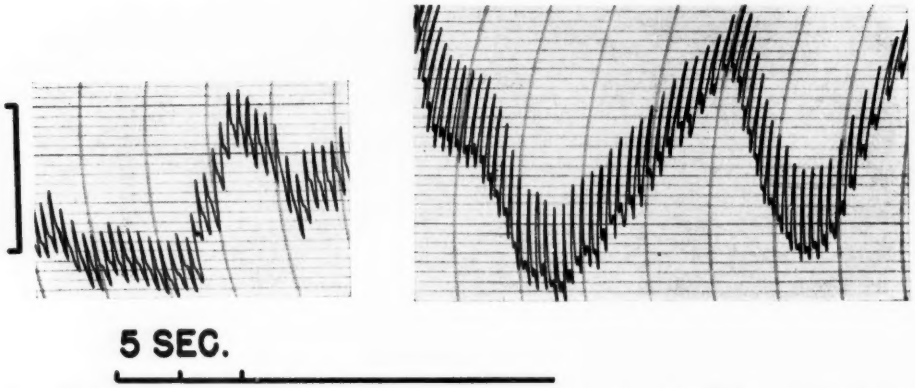

Fig. 3. Toetip plethysmograms from a hypertensive patient, before and after nitroglycerine. Control tracing on the left. Note the increase in volume pulse amplitude, the increase in alpha wave amplitude, and the fall in the position of the dicrotic notch after the administration of nitroglycerine.

ing diffuse vascular disorders such as arteriosclerosis and arteriolosclerosis (Fig. 2).

It seemed reasonable to assume that the plethysmographic changes noted in the presence of these diseases might also be induced by sustained vasospasm. The correctness of this assumption was borne out by certain preliminary observations which indicated that prognostications based only upon the contour of the volume pulse wave and upon the alpha waves were not sufficiently exact for predicting the effects of sympathectomy. Thus it seemed evident that preoperative appraisals of surgical results could be attained only after ascertaining the vasospastic component which might exist in each instance of hypertension. Fourteen hypertensive patients were accordingly subjected to both direct and reflex conversive heating. This was always followed by a pronounced increase in the total volume of the fingertip and the toetip, but the changes in the contour and in the amplitude of the volume pulse were inconspicuous and the alterations in both the frequency and amplitude of the alpha waves were inconstant. These variable results could not be correlated with the postoperative changes in blood pressure and therefore appeared to indicate that it would be necessary to employ other vasodilating procedures. Previous experiments had demonstrated that nitroglycerine induced profound plethysmographic alterations in normal persons; these consisted of changes in both contour and amplitude of the volume pulse and alterations in the frequency and in the amplitude of the alpha waves. These observations together with the experi-

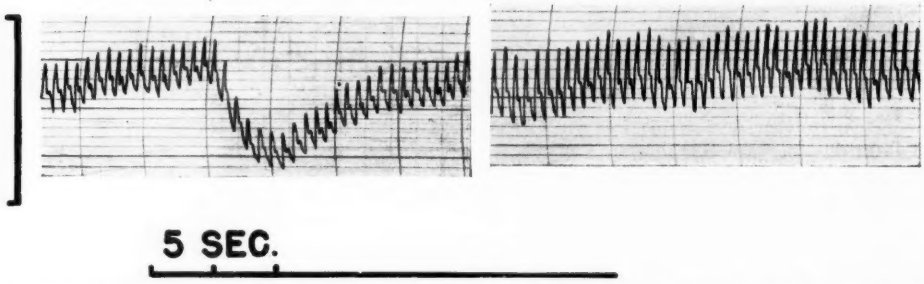

Fig. 4. Toetip plethysmograms from a hypertensive patient before and after nitroglycerine. Control tracing on the left. Note that the administration of nitroglycerine is followed by an increase in the volume pulse amplitude only.

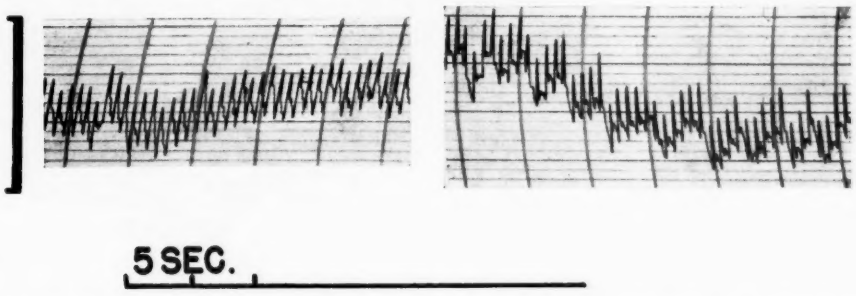

Fig. 5. Toetip plethysmograms from a hypertensive patient before and after nitroglycerine. Control tracing on the left. Note that following nitroglycerine the primary change is manifested by a fall in the position of the dicrotic notch.

ences of previous investigators which demonstrated that the administration of nitrites may be followed by vasodilatation resulting from a direct effect upon the smooth muscle of the smaller blood vessels, suggested the use of nitroglycerine as a means of reducing vasomotor tone. Accordingly this drug was administered sublingually in doses ranging from 1/100 to 1/150 grain to 98 hypertensive patients. The plethysmographic changes which ensued could be classified into a number of broad categories; in one there was an increase in volume pulse amplitude and a fall in the position of the dicrotic notch (Fig. 3), in another the amplitude increased but the pulse contour remained unchanged (Fig. 4), in a third a characteristic lowering in the location of the dicrotic notch was observed (Fig. 5), but there was either no change or an actual decrease in the amplitude of the volume pulse, in a fourth the volume pulse amplitude decreased and the dicrotic notch fell (Fig. 6), and in the fifth no plethysmographic alterations were evident. These distinctions are not absolute. For example the extent to which both the dicrotic notch descends and the volume pulse amplitude increases may be slight, or moderate or marked. Ordinarily an increase in the amplitude of the volume pulse deflections was accompanied by an increase in the frequency and in the amplitude of the alpha waves. Exceptions to this relationship were encountered and subsequent results indicated that from the prognostic viewpoint, alterations in alpha waves were not as significant as were corresponding changes in the volume pulse waves.

Usually the plethysmographic patterns of corresponding digits in each individual were similar. On occasion they differed markedly in that the amplitude of the various intrinsic volume deflections both before and after vasodilatation were much greater on one side than on the other (Fig. 7). It is evident that differential plethysmographic patterns of this type indicate the existence of structural vascular disease. Such findings also demonstrate that

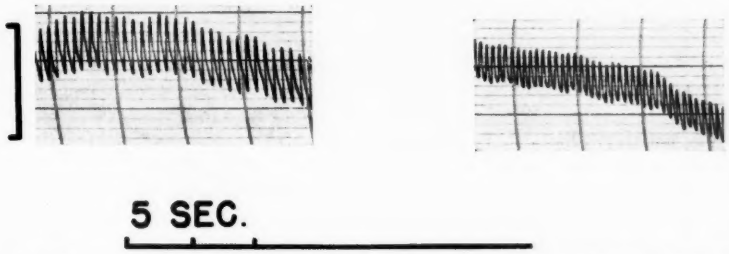

Fig. 6. Toetip plethysmograms from a hypertensive patient before and after nitroglycerine. Control tracing on the left. Note that after nitroglycerine the volume pulse amplitude decreased while the dicrotic notch fell to the baseline.

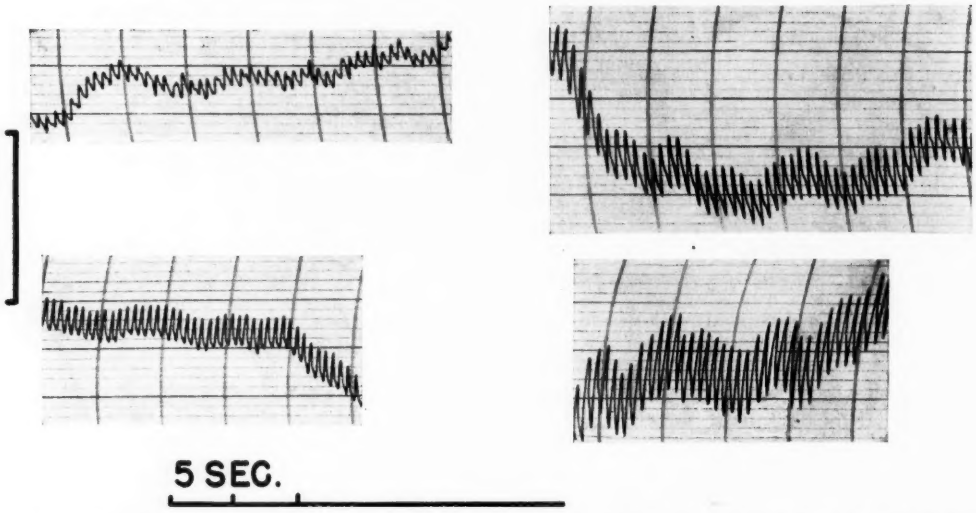

Fig. 7. Toetip plethysmograms from a hypertensive patient. Upper tracings from the left and right great toes before lower tracings from the same toes after nitroglycerine. Note the marked differences in both sets of tracings.

the rate at which the pathological alterations in the different vascular beds develop, may vary considerably.

The change in the volume fluctuations of the digits which follow the administration of nitroglycerine has been employed as an index for estimating the functional occlusive, as opposed to the structural occlusive component in each instance of hypertension. Since the functional integrity of a vascular bed may be measured by its ability to dilate, the absence of any plethysmographic change after the administration of nitrites presumably indicates that fixed organic vascular disease is present. A decrease in the volume pulse amplitude even when coupled with a decline in the position of the dicrotic notch is evidence that structural alterations in the blood vessels have developed. The reduced amplitude may be explained by assuming that a portion of the circulating blood volume has been diverted temporarily to relatively uninvolved areas in which the peripheral resistance has been reduced by pharmacologic vasodilatation. Conversely, an increase in the volume pulse amplitude especially when accompanied by characteristic changes in the contour of the volume pulse and by increases in the amplitude of the alpha waves strongly suggests the presence of vasospasm; the magnitude of these alterations will represent the relative importance of increased vasomotor tone in each instance of hypertension.

At this point it may be stated that prognostic usefulness of the plethysmographic method has been established by the operative results; the procedure was originally designed as a method of study of the finer circulatory dynamics in hypertension and not as a means of selecting patients for sympathectomy. It is only as a result of analyzing the plethysmographic data and contrasting these with changes in arterial pressure after sympathectomy that there is justification for the statement that the criteria which have been described may be regarded as an index of postoperative results. Hence the present report details only the studies of those hypertensive patients who underwent operation.[1] It is evident from this study that the presence of factors such as cardiac enlargement, electrocardiographic changes, severe grades of hypertensive retinopathy, urinary abnormalities, and diminished renal function cannot by themselves, be considered as absolute indicators of poor surgical results. Fur-

[1]Detailed table of essential physical and laboratory data will be found in Table I in reprints of this article.

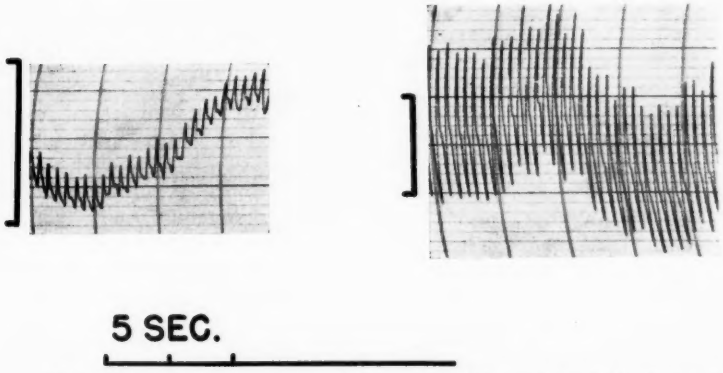

Fig. 8. Toetip plethysmograms from the left great toe before and after left lumbodorsal sympathectomy. Tracing on the left before operation. Note the pronounced increase in amplitude which followed sympathectomy.

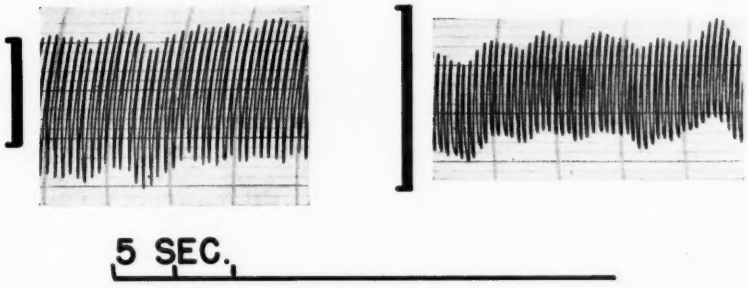

Fig. 9. Toetip plethysmograms following lumbodorsal sympathectomy. Tracing on the left obtained before and that on the right obtained after nitroglycerine administration. Note the decrease in the volume pulse amplitude which followed the administration of nitroglycerine.

thermore the data suggest that an excellent therapeutic response may be expected in appropriately selected hypertensive patients who are more than 50 years old.

The sodium amytal test was performed in 23 of the 30 patients subjected to operation. The findings[1] have been compared with the plethysmographic changes after nitroglycerine and with the arterial pressure after sympathectomy. The contrast between the amytal test and the plethysmographic method is apparent. By the amytal test an accurate forecast was made in but 8 of the 23 patients; while by the plethysmographic method a correct result was prognosticated in 27 of the 30 patients. Plethysmography led to erroneous conclusions in 3 patients.

[1]See Table II in reprints.

THE PLETHYSMOGRAM FOLLOWING SYMPATHECTOMY

After sympathectomy, vascular tone is dependent upon local metabolic and environmental requirements, and upon the concentration of circulating humoral vasoconstrictor and vasodilator substances (3). Variations in volume pulsations may therefore be quite pronounced unless observations are made under relatively constant conditions. Aside from this, interruption of the sympathetic outflow to an extremity whose vascular bed has been in a state of increased tonus is followed by a maximal increase in the height of the volume pulse, by a loss of vasoconstrictor reflexes, and by a disappearance of the alpha waves (Fig. 8). After attempted vasodilatation by nitroglycerine, the volume pulse amplitude either remains

unchanged or it actually decreases (Fig. 9). Conversely the failure to elicit these changes after sympathectomy is presumptive evidence that complete vascular denervation has not been attained. This observation is of importance since it may account for the poor operative results in patients deemed suitable for sympathectomy by the previously described plethysmographic criteria. As examples may be cited two of the patients in the series who, although plethysmographically considered as excellent candidates, developed no reduction in the level of the systemic arterial blood pressure after sympathectomy. The plethysmograms postoperatively were essentially similar to those obtained preoperatively in that large amplitude alpha waves persisted, nitroglycerine continued to induce a distinct increase in the volume pulse amplitude, and reflex vasoconstrictor activity could still be demonstrated. From a consideration of these facts it appears that the plethysmographic method may offer means of evaluating the extent and adequacy of operations on the sympathetic nervous system. Therapeutic implications are apparent.

Digital plethysmography has been of additional value in that by this method we have been able to demonstrate objectively the basis for the acroparaesthesias in the fingers which not infrequently follow sympathectomy. Fingertip tracings in these cases have revealed an increase in vasomotor tone as evidenced by the fact that the volume pulse amplitude postoperatively is reduced when compared with the amplitude preoperatively.

DISCUSSION

It is now generally believed that there are no structural vascular alterations until the later stages of "essential hypertension" are reached and that elevations in the level of the diastolic pressure are induced by increased vasoconstrictor activity mediated through humoral or neuropressor mechanisms. That the increase in total effective peripheral resistance may be primarily related to augmented vasomotor tone in selected areas of the systemic arteriolar bed is also generally accepted. Since bilateral sympathectomy aims at reducing the vasomotor tone of the splanchnic area and of the lower extremities, in theory at least, its effectiveness will be limited by the following factors, namely, that segments of the arteriolar bed other than the splanchnic area and the lower extremities are responsible for the increased peripheral resistance, that the increased resistance is induced by humoral rather than by neurogenic mechanisms, and that structural alterations have developed. A consideration of these facts enables one to understand why inferences based only upon a simple measure of the arterial pressure after the administration of the various pharmacologic agents which have been advocated, so frequently lead to erroneous conclusions. For similar reasons the inherent fallacy of basing prognostications upon the presence or absence of retinal, urinary, electrocardiographic and roentgenological changes is apparent. While as a generalization it is true that the existence of such alterations is indicative of an advanced stage of hypertension, the results of our study demonstrate that each patient must be evaluated individually and that the occurrence of these organ changes is not incompatible with excellent operative results. By the same token, the fact that a hypertensive patient is past the age of 50 years means that in all probability he has had an elevated blood pressure for a longer period than a younger patient, and that the likelihood of generalized vascular changes has correspondingly increased. As with the other factors mentioned this concept is only valid in broad terms, and the importance lies in exactly individualizing each patient. We are therefore forced to the conclusion that the indications for operation should be essentially clinical, and that the reliance on the prognosis of operation can be placed on microplethysmographic examination.

At the present time there is no practical method that is available to evaluate the factor of splanchnic vasoconstriction, but in contradistinction to the other procedures which have been previously advocated, microplethysmography can offer accurate, objective information concerning the vascular state of at least a portion of the arteriolar bed which is to be denervated by sympathectomy. As Goetz has emphasized, digital plethysmography evaluates the "ultimate" circulation, and although there can be no argument with the technique, a logical and valid criticism of the procedure

may be based on the use of nitroglycerine, especially since the nitrites and sympathectomy induce vasodilatation by entirely different mechanisms. We are cognizant of this possible source of error, and are analyzing this problem by contrasting the plethysmographic changes following the use both of nitroglycerine and tetraethylammonium. The results of these experiments are to be presented in a future report.

SUMMARY AND CONCLUSIONS

1. A microplethysmographic method is described for selecting hypertensive patients who are to benefit from sympathectomy. This is based on the use of a new direct ink recording photoelectric microplethysmograph.

2. The procedure entails an analysis of the volume changes occurring in the phalanges before and after the attempted release of vasomotor tone by nitroglycerine.

3. It was demonstrated that one of five volume alterations follow the sublingual administration of nitroglycerine, and that satisfactory operative results occur only in those patients who develop a pronounced increase in the volume pulse amplitude after nitrite ingestion. The simultaneous occurrence of an increase in the amplitude and in the frequency of the alpha waves is a good prognostic sign, but the absence of such changes does not preclude a significant postoperative reduction in the arterial pressure.

4. The plethysmographic method predicted the operative results correctly (whether favorable, 20 patients: or unfavorable, 7 patients) in 27 of the 30 subjects. In contrast the sodium amytal test led to accurate conclusions in 8 of 23 patients.

5. The inherent fallacy of the amytal test and of the other criteria currently employed as indices of operability is discussed.

6. Aside from its usefulness as a means of selecting patients for operation, microplethysmography has the added value of being able to estimate the postoperative extent and completeness of sympathectomy.

7. A possible error in the procedure is mentioned. This depends upon the use of nitroglycerine as a vasodilator.

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EFFECTS OF SUBLETHAL HEMORRHAGE IN NORMAL DOGS AND IN DOGS PREVIOUSLY TRANSFUSED WITH WHOLE BLOOD

RAY SEAVERS, M.D., and PHILIP B. PRICE, M.D., F.A.C.S., Salt Lake City, Utah

THE changes occurring in the circulating blood of man and animals following hemorrhage have been fairly well investigated. In an experimental investigation of hemorrhagic shock, Price and his associates (12) have demonstrated what changes occur in the circulating blood of dogs following acute, lethal hemorrhage. It is generally believed that following rapid severe hemorrhage there is a decrease in plasma protein concentration and in hemoglobin concentration proportional to the amount of fluid shifted into the blood stream. Elman (10) stated that after hemorrhage the most pronounced hemodilution occurred within the first hour and continued for 72 hours. Price reported (12) that following massive bleeding (34 c.c. per kgm.) there was an influx of fluid into the blood stream of 3.4 cubic centimeters per kilogram and an influx of red cells amounting to 3.8 cubic centimeters per kilogram within 5 to 6 hours. Although Price noted no increase in total circulating plasma protein mass following fatal hemorrhage in normal dogs, he found that after a single sublethal hemorrhage the total plasma protein mass returned to normal in 48 hours and plasma volume returned to normal in 24 hours. Elman (8) stated that following sublethal hemorrhage correction of the lost albumin fraction began in the first 6 hours and was still incomplete at 7 days. He noted also (9) that in fasting dogs which were bled rapidly and in which the blood was replaced with saline there was a drop of 20 to 22 per cent in protein concentration. This value did not change for 6 hours indicating that there was no rapid mechanism for the restoration of serum protein concentration. Cutting found that after the removal of 40 per cent of the blood of a rat the total protein mass returned to the original level in 12 hours. Calvin (4) stated that following subacute hemorrhage in a dog there was evidence of movement of fluid into the circulation within a few hours and that protein (primarily albumin) entered with this fluid. Beattie (3) concluded that within 2 hours of hemorrhage, in cats anesthetized with nembutal, there was evidence of movement of plasma proteins into the blood stream.

Relatively little attention has been paid, however, to the changes which occur in the circulating blood of animals following hemorrhage when those animals have been previously transfused with whole blood. Since preoperative transfusion of patients in anticipation of a sanguineous operative procedure is common practice, it was thought that transfusion of experimental animals prior to rapid, sublethal hemorrhage, and comparison of the posthemorrhagic response to that of control dogs subjected to similar hemorrhage might shed some light on the efficacy of the practice. This paper is a report of an experimental study of that sort.

METHODS AND CALCULATIONS

The first group of dogs were normal healthy animals with an average weight of 17.6 ± 1.2 kilograms. This group of animals was used as controls.

They were anesthetized lightly with intravenous, 5 per cent sodium pentobarbital solution and were prepared for the experiment by cannulating the carotid artery, intubating the trachea, and exposing the femoral vein. Following a "basal" period of 1 to 2 hours, during which time preliminary determinations were made, the dogs were bled rapidly from the carotid artery. The effects of this bleeding were then studied for 5 hours.

From the Department of Surgery, University of Utah Medical School, Salt Lake City, Utah.

Aided by a grant for the study of Surgical Shock from the U.S. Public Health Service.

The second group, the experimental animals, consisted of normal healthy dogs averaging 17.0±1.1 kilograms. They were prepared in the same manner as the first group except that following the "basal" period they were transfused with well matched, citrated, whole blood which had been freshly drawn from healthy dogs. After transfusion, studies were made for a period of 3 to 5 hours. The dogs were then bled rapidly from the carotid artery and the various determinations made hourly for 4 to 12 hours.

All determinations were made by means of standard methods and procedures which have been described more completely elsewhere (12, 14). In brief, however, the dye method (T-1824), with Price and Longmire's (13) modification of the Gibson and Evelyn technique was used for plasma volume determinations, and the falling drop method of Barbour and Hamilton checked occasionally by Kjeldahl measurements was used for protein concentration determinations.

Statistical analysis consisted of computing the standard error of all means and of testing the significance of those means. When it was desired to show a significant difference between means, the standard error of the difference between means was tested for significance.

RESULTS

This study included 2 series of experiments. The first, a control study, consisted of 6 normal dogs which were bled rapidly from the carotid artery and in which the posthemorrhagic response was studied for 5 hours. The bleeding required 3 to 5 minutes and averaged 15.0±.7 cubic centimeters per kilogram.

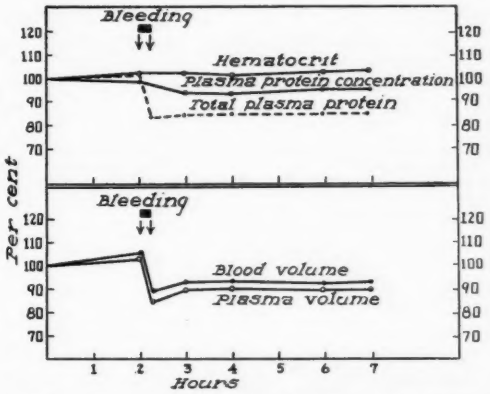

Fig. 1. Control study. Effects of rapid sublethal hemorrhage in normal dogs anesthetized with sodium pentobarbital. Mean values of 6 experiments.

The second series consisted of 10 dogs which were transfused before being bled. Five of these dogs were splenectomized in order to eliminate the factor of the expansile canine spleen and its consequent effects as an erythrocyte "store." In general, little difference was noted, however, between the splenectomized and nonsplenectomized dogs, except in the response of the total hemoglobin mass after bleeding.

Each experiment in the second series consisted of 3 parts. First, there was a "basal" period prior to transfusion during which preliminary studies were made. These initial determinations, made during the first 1½ to 2 hours, represent normal values for the animal and hereafter will be designated "basal" values. The second part of the experiment began with the start of the transfusion, which required

TABLE I.—AVERAGE VALUES DETERMINED BEFORE AND AT HOURLY INTERVALS AFTER RAPID SUBLETHAL HEMORRHAGE IN NORMAL DOGS ANESTHETIZED WITH SODIUM PENTOBARBITAL

	"Basal"	Immediately before hemorrhage observed values	Immediately after hemorrhage expected values	1 hour after hemorrhage	2 hours after hemorrhage	4 hours after hemorrhage	5 hours after hemorrhage
Hematocrit	42.2 ±2.1	43.4 ±1.8		43.1 ±1.9	42.5 ±1.8	43.2 ±1.7	44.0 ±2.2
Circulating cell volume (c.c. per kgm.)	40.6	44.8	38.6	39.6	38.7	38.7	38.7
Plasma protein concentration (grams per cent)	6.25± .15	6.20± .18		5.90± .17	5.89± .15	6.02± .16	6.00± .14
Total plasma protein mass (grams per kgm.)	2.83± .27	2.89± .22	2.33± .22	2.40± .18	2.41± .17	2.40± .19	2.41± .20
Plasma volume (c.c. per kgm.)	45.5 ±1.4	47.2 ±1.6	38.4 ±1.5	41.0 ±1.8	41.3 ±1.8	40.7 ±2.0	40.9 ±2.1
Blood volume (c.c. per kgm.)	86.1 ±3.2	92.0 ±2.8	77.0 ±2.7	80.6 ±2.5	80.0 ±2.6	79.4 ±2.4	79.6 ±2.4

TABLE II.—AVERAGE VALUES OF THE CITRATED BLOOD USED FOR THE 10 TRANSFUSIONS

Amount of blood given per kgm. of recipient	15.4 ±1.2 c.c.
Amount of plasma given per kgm. of recipient	9.5 ± .8 c.c.
Protein concentration	6.89± .19 grams per cent
Hemoglobin concentration	13.4 ±1.7 grams per cent
Hematocrit	41.7± .5
Amount of protein given per kgm. of recipient	.65± .05 gram
Amount of hemoglobin given per kgm. of recipient	2.08± .21 grams

approximately 1 hour, and terminated at the time of bleeding. The last value determined just before bleeding is referred to as the "prehemorrhage" value and marked the beginning of the third, or "posthemorrhage" portion of the experiment. After bleeding, which required but 3 to 5 minutes and averaged 16.4 ± 1.2 cubic centimeters per kilogram, determinations were made at hourly intervals until 4 hours or more had elapsed.

The term, "expected" value, has been used to refer to those values calculated from the previous value minus the amount of blood, plasma, protein, lost by hemorrhage. For example, the "expected" blood volume after hemorrhage was calculated by subtracting from the "prehemorrhage" blood volume the amount of blood taken from the carotid artery during the bleeding.

Changes occurring after hemorrhage in normal dogs. The changes which occurred in the circulating blood of the 6 animals comprising the control series are given in Table I, and a graphic representation of some of those changes is shown in Figure 1.

Following hemorrhage the dogs on the average gave little if any evidence of hemodilution (Fig. 1). The small changes which occurred were not significant. Variations in hemoglobin concentration paralleled those in hematocrit.

There was no significant alteration in circulating cell volume from that "expected" following hemorrhage. No change in relative red cell size could be detected.

All dogs showed some reduction of plasma protein concentration after hemorrhage. The average 4 to 5 per cent reduction was, however, not statistically significant.

Following hemorrhage, return of small amounts of plasma protein to the circulation could be detected in most of the control animals. Five of the 6 dogs showed a slight increase in total protein mass above that "expected" after hemorrhage, but the average increase of 1.1 grams of protein (2.5 per cent of the entire protein mass) was not significant.

Blood volume showed an increase of 2.6 cubic centimeters per kilogram 4 hours after hemorrhage. This also was not a significant increase.

Changes occurring during and immediately following transfusion. Since the results of whole blood transfusions in normal dogs have been previously presented (14), the changes

TABLE III.—AVERAGE VALUES DETERMINED BEFORE TRANSFUSION, BEFORE HEMORRHAGE (3 TO 5 HOURS AFTER TRANSFUSION), AND AT HOURLY INTERVALS AFTER HEMORRHAGE OF 10 DOGS TRANSFUSED WITH CITRATED WHOLE BLOOD THEN BLED FROM CAROTID ARTERY

	"Basal"	"Pre-hemorrhage"	"Expected"	1 hour after hemorrhage	2 hours after hemorrhage	4 hours after hemorrhage
Hemoglobin (grams per cent)	15.4 ± .4	18.2 ± .3		17.3 ± .5	17.2 ± .4	17.2 ± .3
Hematocrit	46.5 ±1.6	56.3 ±1.2		53.4 ±1.6	52.7 ±1.5	53.4 ±1.3
Total hemoglobin mass (grams per kgm.)	12.0 ± .5	15.0 ± .4	11.6 ± .4	11.6 ± .4	11.3 ± .5	12.0 ± .4
Protein concentration (grams per cent)	6.88± .16	7.24± .18		6.79± .08	6.80± .15	6.72± .12
Total protein mass (grams per kgm.)	3.08± .27	2.89± .09	2.23± .08	2.34± .03	2.33± .03	2.43± .04
Plasma volume (c.c. per kgm.)	45.1 ± .8	40.0 ±1.3	30.1 ±1.2	34.4 ±1.0	34.2 ±1.1	36.0±1.2
Blood volume (c.c. per kgm.)	78.1 ±1.7	82.5 ±1.2	63.7 ±2.1	67.4 ±2.1	66.3 ±2.4	70.2 ±2.2
Blood pressure (mm. of Hg.)	154 ±5	150 ±7		139 ±5	139 ±5	138 ±5
Pulse	168 ±9	155 ±6		166 ±8	170 ±9	174 ±7
Temperature	99.8 ± .4	101.3 ± .7		101.8 ± .7	102.1 ± .7	102.4 ± .6

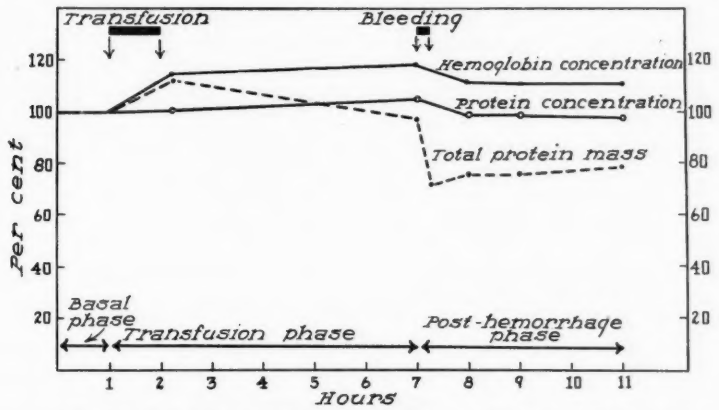

Fig. 2. Effects of rapid sublethal hemorrhage in normal anesthetized dogs previously transfused with whole blood. Mean values of 12 experiments.

occurring in the second series of experiments from the time of transfusion to the time of hemorrhage will not be reported here in detail. Average values of the citrated blood used for the transfusions are given in Table II. Table III gives average "basal" and "prehemorrhage" values showing alterations occurring during transfusion phase of second series. Briefly, the following changes were evident:

Three to 5 hours after transfusion, at the time of bleeding, average hemoglobin concentration was increased 18 per cent; average hematocrit was increased 21 per cent; total circulating hemoglobin mass and circulating cell volume were increased 25 per cent and 26 per cent respectively although the expected increase for both hemoglobin and cell volume was only 17 per cent; plasma volume was decreased 11 per cent and blood volume was increased 5 per cent; total circulating protein mass was decreased 6 per cent, representing a loss of protein equivalent to that injected (.65 gram per kgm.) and a further loss of .18 gram per kilogram.

Changes occurring after hemorrhage in dogs previously transfused with whole blood. Average values for hemoglobin concentration, hematocrit, total hemoglobin mass, plasma protein concentration, total plasma protein mass, plasma volume, blood volume, pulse, temperature and blood pressure following hemorrhage are given in Table III.

Following hemorrhage, all dogs showed some degree of hemodilution (Fig. 2). Average hemoglobin concentration of 18.2 grams per cent was reduced to 17.3 grams per cent 4 hours after hemorrhage. This represents an average decrease of 5 per cent. Although this average decrease was not statistically significant the range was fairly wide and a few dogs showed considerable hemodilution. Most of the hemodilution took place during the first hour.

One hour after hemorrhage hematocrit decreased from 56.3 to 53.4, and 4 hours after hemorrhage the hematocrit was 53.4. This represents an average decrease of 5 per cent.

Varying responses were noted in total hemoglobin mass. After hemorrhage, average total hemoglobin mass was the same as the average "expected" value (Fig. 3); in general, however, an increase in total hemoglobin mass was noted in the nonsplenectomized dogs and a slight decrease was observed in the splenectomized dogs. The same changes were observed in circulating cell volume. There was no significant alteration of the relative red cell size following hemorrhage.

Protein concentration (Fig. 2) decreased 6 per cent 1 hour following hemorrhage, and by 4 hours was reduced 7 per cent below the prehemorrhage value. Although reduction in plasma protein concentration was a constant finding following hemorrhage the average change was not statistically significant.

One hour following hemorrhage, total circulating protein mass (Fig. 2) increased above the "expected" value in 7 of the 10 dogs. In 2 experiments the influx of plasma protein into the blood stream was sufficient to return the plasma protein mass to its prehemorrhage value; however, the plasma protein increase observed in the other experiments was not great. Also, the decrease in plasma protein below the expected value observed in 3 experiments was very slight. The average increase in plasma protein mass following hemorrhage was not significant.

An increase in plasma volume over and above the expected volume occurred in 9 of the 10 dogs 1 hour after hemorrhage. Average increase 1 hour after hemorrhage was 4.3 cubic centimeters per kilogram or 9 per cent above the expected plasma volume. Four hours after hemorrhage plasma volume was increased 5.9 cubic centimeters per kilogram or 13 per cent above the "expected" volume. These changes are illustrated in Figure 3. In 2 experiments plasma volume was increased above the prehemorrhage value, thus returning to the circulation an amount of fluid more than equal to the volume of plasma lost during hemorrhage. This average increase in plasma volume was statistically significant.

One hour and 4 hours after hemorrhage, 6 of the 10 dogs showed an increase in blood volume above the "expected" volume. In 1 experiment blood volume returned to the prehemorrhage level at 4 hours. In those animals which showed a decrease in blood volume below the "expected" value there was no instance in which the decrease exceeded 5 per cent; in fact, most of these animals showed only a very slight decrease. The average increase of 6.5 cubic centimeters per kilogram at 4 hours (Fig. 2) was not significant.

During hemorrhage blood pressure fell precipitously from an average 150 millimeters of mercury to 50 to 60 millimeters of mercury. Recovery was rapid, however, and usually blood pressure returned to within range (i.e. within 1 standard deviation) of the pretransfusion value in 15 minutes.

Following hemorrhage, there was usually a tendency for the pulse rate to increase, but not enough to be considered significant.

There was a steady rise in temperature throughout the experiments. An average increase of 1.5 degrees from the start of the experiment to the time of hemorrhage was noted, and a further rise of 1.3 degrees from the time of hemorrhage to the end of the experiment was observed.

Respiratory rate, respiratory volume, and oxygen uptake were determined in 3 animals. No significant changes were noted in any of these values following hemorrhage.

DISCUSSION

The most striking change occurring in the circulating blood following hemorrhage was prompt hemodilution of greater or less degree due to influx of fluid into the circulation (Figs. 1 and 3). Although in the control animals some fluid entered the circulation after hemorrhage, it was not in significant amounts; in the dogs that had been transfused just before hemorrhage, however, significant amounts of fluid did enter the circulation. A volume of fluid equivalent to 9 per cent of the original plasma volume was added to the circulation within the first hour, on the average, and by the end of 4 hours a volume of fluid equivalent to 13 per cent of the original plasma volume had entered the circulation. In the matter of fluid shifts, therefore, there appears to be a distinct difference between the normal dogs and those that had been transfused just before hemorrhage. However, the size of these fluid translocations varied considerably, and it is possible that these shifts depended more on the status of body hydration before the experiment than on the amount of blood added by transfusion. Although most of the fluid entered the circulation during the first hour, in several experiments fluid continued to enter the circulation until 4 hours after hemorrhage.

In both series of experiments this influx of fluid following hemorrhage was sufficient to be reflected as changes in hematocrit, hemoglobin, and plasma protein concentration. These values showed an immediate decrease during the first hour. The influx of red blood cells, which was about 4 per cent of the original total mass in both series, was sufficient to forestall further apparent hemodilution after the first hour.

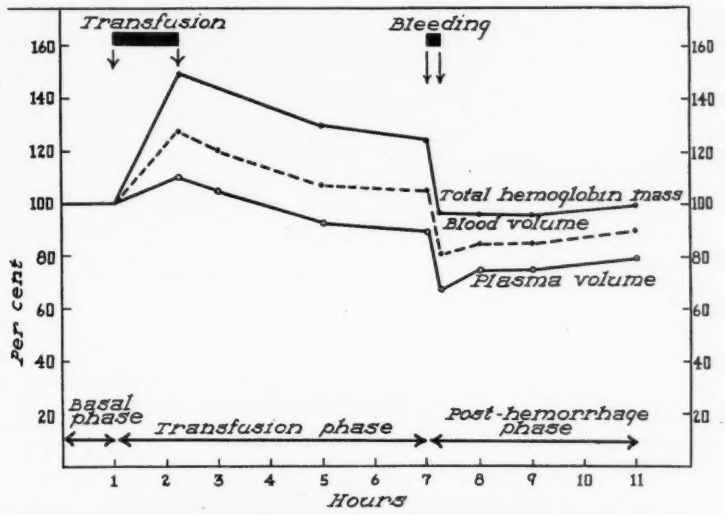

Fig. 3. Effects of rapid sublethal hemorrhage in normal anesthetized dogs previously transfused with whole blood. Mean values of 12 experiments.

Since protein concentration remained stable after the first hour following bleeding, and plasma volume continued to increase, it seems obvious that protein must have entered the circulation to maintain this concentration. Although in those dogs previously transfused, the average of 3.4 grams of protein (6.5 per cent of original mass), added to the circulation after hemorrhage, was not a statistically significant amount, it still seems reasonable that there exists some mechanism which enables the body to replace protein lost from the blood stream by hemorrhage. A likely possibility is that of plasma protein storage. This seems more probable when one considers the fact that 2 of the 10 dogs returned 10 to 11 grams of protein to the circulation whereas 3 dogs showed no return of protein at all. Such wide differences in response are possibly in part influenced by the size of the plasma protein stores, and this seems to offer some evidence to support the contention that plasma protein stores do exist. It is also possible that the magnitude and rapidity of the fluid translocations following hemorrhage, through subsequent lowering of plasma protein concentration, may serve as the impetus for the discharge of protein to the circulation. Whether this impetus is purely mechanical or whether it is brought about by some intermediate hormonal action is a matter of conjecture. Calvin and others (4) have shown that this protein which is returned to the circulation after hemorrhage is mainly albumin.

The existence of plasma protein stores appears to be fairly well established (2, 5). There is, however, no definite agreement as to the site of storage. Some (11) believe the liver to be primarly concerned, whereas others (6) assign this function, or at least the pathway for the return of plasma protein to the circulation, to the lymphatic system. Some evidence has been offered previously (14) suggesting that the protein which disappears from the circulation following transfusion enters into protein storage "depots," that is, general reserve protein stores such as have been shown to exist by Whipple (11).

In our second series of experiments we found that 3 to 5 hours following transfusion a significant amount of protein (.83 gm. per kgm.) disappeared from the circulation. However, 4 hours after hemorrhage, which removed an average of .68 gram of protein per kilogram, an average of only .20 gram had been returned to the circulation. Both the

control animals and the animals previously transfused showed considerable variation in response to acute plasma protein loss. As has been stated, some of the dogs quickly added as much as 10 to 11 grams of protein to the circulation; others none at all. The average response by control and previously transfused dogs was not significantly different.

It would appear that rapid influx of plasma protein to the blood stream following bleeding depends upon at least 3 factors: (1) acute need, (2) availability of protein in "stores," and (3) the original concentration of protein in the plasma. Since the acute need for protein was standardized in all our animals, and since there was no consistent relationship in our experiments between original plasma concentration and the amount of protein returned to the plasma, variations in response are attributed, in a large part, to variations in availability of suitable "stored" plasma protein. Inasmuch as there was little difference in response to hemorrhage between our control and transfused dogs, it follows that the transfusions given prior to bleeding probably did not add protein to protein "stores" in such a form that it could be called upon in case of acute need.

CONCLUSIONS

1. Results of rapid, sublethal hemorrhage in normal dogs and in dogs previously transfused with whole blood have been presented.

2. A blood transfusion given a few hours before sublethal hemorrhage in normal dogs did little to influence the posthemorrhagic response except to supply an extra number of red blood cells and possibly a small fluid reserve.

3. Evidence is presented to support the existence of plasma protein stores.

4. The protein that was given with a blood transfusion to a normal dog quickly left the circulation. There is reason to believe that part of it at least entered plasma protein "depots."

5. When a previously transfused animal was subjected to an acute sublethal hemorrhage, as a rule, only a small portion of the needed plasma protein was added promptly to the circulation following the hemorrhage.

6. It seems probable, therefore, that the plasma protein which disappeared from the circulation following transfusion of normal dogs did not, in most cases, enter protein stores in such a form as to be available for immediate recall to the circulation following rapid sublethal hemorrhage.

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THE NATURE OF POSTOPERATIVE HYPOPROTEINEMIA IN PATIENTS WITH GASTROINTESTINAL CANCER

IRVING M. ARIEL, M.D., Minneapolis, Minnesota

PATIENTS with gastrointestinal cancer frequently present variable degrees of emaciation and cachexia. Because of the high incidence and great mortality from gastrointestinal cancer, a study was instituted to investigate some of the metabolic abnormalities that might exist. This report deals with the incidence and degree of hypoproteinemia in patients with gastrointestinal cancer and emphasizes the effect of surgery upon certain phases of nitrogen metabolism.

PREOPERATIVE PLASMA PROTEIN CONCENTRATION IN PATIENTS WITH GASTRIC CANCER

One hundred patients with gastrointestinal cancer have been studied as to the state of their serum proteins. Serum protein for normal individuals has been found to range from 6.5 to 7.4 grams per cent. The average is 6.9 grams per one hundred cubic centimeters with a standard deviation of ± 0.47 gram per cent. In sharp contrast, the average serum protein concentration in patients with gastrointestinal cancer is 6.2 grams per cent with a standard deviation of ± 0.67 gram per cent. Of the 100 patients examined 59 were found to have abnormally low levels (Charts 1 and 2) (8).

The cause of hypoproteinemia is not entirely clear. Several possibilities present themselves; namely, (1) deficient diets, (2) repeated hemorrhage, (3) a defect in the absorption of amino acids, (4) increased catabolism of the protein, or (5) some metabolic abnormality which prevents the synthesis of serum proteins.

Dietary deficiency. In an attempt to ascertain the role played by a deficient dietary intake in the production of hypoproteinemia, the patients were divided into five groups according to the degree of dietary deficiency. The mean serum protein level and the standard deviation were computed for each group.

The distribution of the serum protein determinations was plotted against variations in diet to show what effect, if any, dietary intake has on the serum protein level. Analysis of the data reveals no statistically significant difference between the means of the different groups which gave evidence of dietary deficiency. All protein values were significantly lower than normal (Chart 3).

It thus becomes apparent that variations in the degree and duration of dietary deficiency do not contribute by themselves significantly to the incidence and degree of hypoproteinemia in patients with gastric cancer.

Relationship of bleeding to hypoproteinemia. Bleeding is an important factor which might be responsible for an abnormal erythron or a low plasma protein concentration. In this series a patient was considered to present evidence of blood loss if he fulfilled any one of the following criteria: (a) history of blood loss (melena, hematemesis, etc.) within 6 months previous to his admission; (b) presence of blood in the stools after 3 days upon a meat-free diet; (c) presence of occult blood within the gastric contents.

Of the 100 patients studied, evidence of blood loss was observed in 42 cases (42%). The arithmetical mean of the serum protein in this group is 6.1 grams per cent. In the other 58 per cent of the series that did not present any evidence of blood loss the arithmetical mean of the serum protein concentration is 6.2 grams per cent (8). The difference between these two groups is not statistically significant; hence it can be concluded that bleeding does not contribute significantly to the low level of the serum protein in this series of patients.

Abnormalities in amino acid metabolism. The possibility presents itself that amino acids are not absorbed properly or that after they are

Parts of this study were performed at Memorial Hospital, New York, New York.

Presented in the Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, New York, New York, September 8 to 12, 1947.

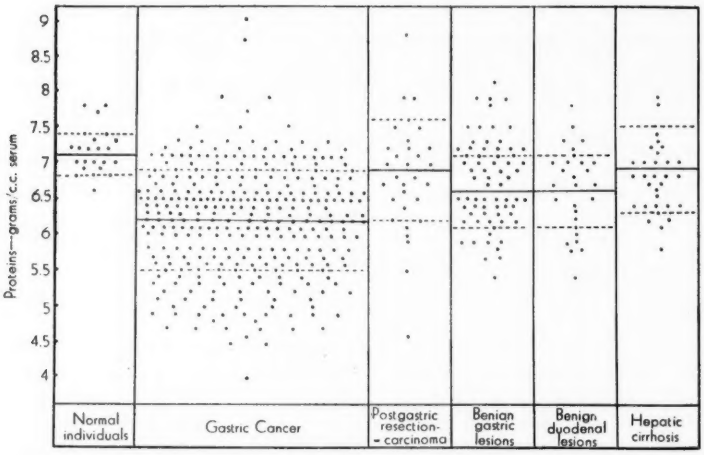

Chart 1. A scatter diagram of total protein concentration per 100 cubic centimeters of serum expressed according to groups with various diseases and one normal control group. The heavy unbroken line represents the mean of each group and the area between the broken lines represents the values between the plus and minus standard deviations from the mean.

absorbed they can not be utilized in a normal manner. This has been substantiated. The ingestion of 25 grams of aminoacetic acid revealed that in 6 controlled subjects the maximum absorption of the compound occurred within the first hour. In contrast to this, in 6 patients with gastrointestinal cancer the peak of absorption was considerably delayed in all. The delayed absorption of the amino acid apparently does not depend merely on the presence of organic gastrointestinal disease for a normal rate of absorption was noted in one patient with atrophic gastritis, in one patient with multiple gastric ulcers, and also one patient with gastric Boeck's sarcoid. These data indicate that the abnormality of absorption may be intimately linked with the presence of cancer (9) (Chart 4). After resection of the cancer, improvement of absorption occurs (Chart 5).

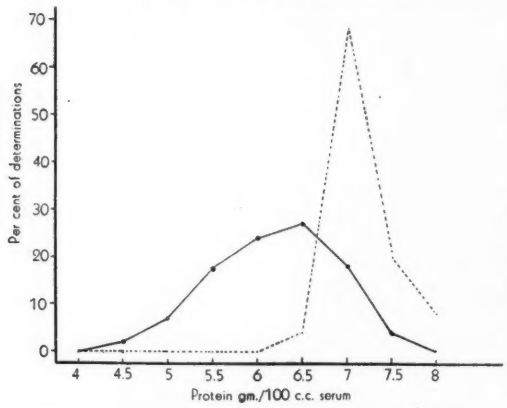

Chart 2. Frequency polygon of total serum protein concentration of patients with gastric cancer compared with normal individuals. —— gastric cancer; ---- hepatic cancer.

The following experiments indicate that in addition to the defective absorption of the amino acid there exists also abnormalities of their metabolism.

a. The ingestion of 25 grams of aminoacetic acid raised the average concentration of serum amino acids in normal individuals by 2.9 milligrams per 100 cubic centimeters. The average increase in the serum of 6 patients with gastrointestinal cancer was 6.6 milligrams (Chart 4). This high level of amino acids in the serum of patients given aminoacetic acid orally has been demonstrated to indicate inability of the liver to utilize that compound at a normal rate (9).

b. Following the intravenous administration of 75 milligrams per kilogram body weight

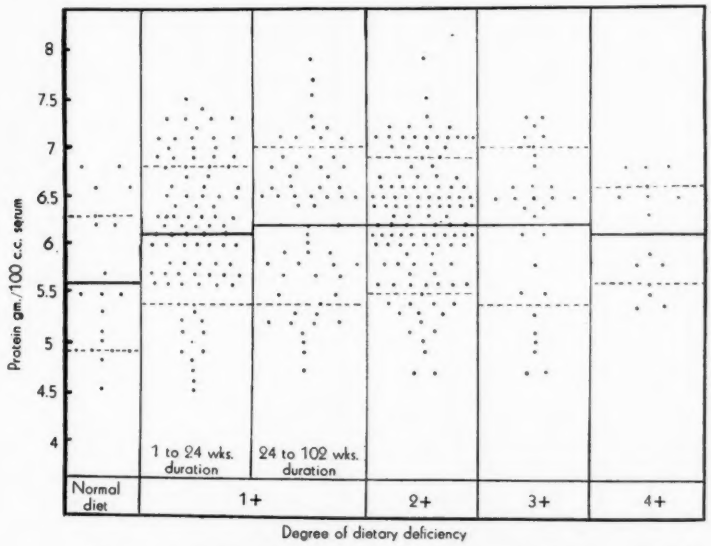

Chart 3. A scatter diagram of total protein concentration per 100 cubic centimeters of serum in patients with gastric cancer referred to degrees of dietary deficiency. The heavy unbroken line represents the mean of each group and the area between the broken lines represents the values between the plus and minus standard deviations from the mean.

aminoacetic acid the analyses of the urinary output of creatine and creatinine in both normal controls and patients with gastrointestinal cancer reveals a marked increase in the amount of creatine and creatinine excreted by 9 normal individuals and 7 patients with benign gastrointestinal disease. The average increase in the normal group was 53.5 milligrams of creatine and 70 milligrams of creatinine, and for the 7 patients with benign gastrointestinal lesions, 27.5 milligrams of creatine and 68.5 milligrams of creatinine.

In sharp contrast to these findings, there was no increased creatine or creatinine in 19 patients with gastrointestinal cancer (2). This fact suggests that glycine, which is the precursor for the formation of creatine, so necessary for muscle metabolism, is not utilized in its normal manner. The muscular weakness noted so frequently in patients with gastrointestinal cancer possibly could be the result of inability of these patients properly to synthesize creatine from glycine.

Hepatic dysfunction. The hypoproteinemia might conceivably be a manifestation of hepatic dysfunction. Since it has been demonstrated that patients with gastrointestinal cancer suffer a high incidence of hepatic dysfunction (3), a comparison was made of the plasma protein concentration of 100 patients with gastrointestinal cancer and of 20 patients with hepatic cirrhosis. The data demonstrate that the degree of plasma protein depletion in patients with gastric cancer was far more severe than in those with hepatic cirrhosis (Chart 6). The albumin protein was the fraction that was depleted always (Chart 7).

Protein catabolism. Studies of the fecal nitrogen output of patients with gastrointestinal cancer revealed no dissimilarity to other groups of patients. The average fecal output is approximately 1 gram of nitrogen per day. Furthermore, the urinary nitrogen of these patients while at rest is not in excess of that of control groups of persons (8). These data demonstrate that there is no increased catabolism of proteins to account for the depleted state.

The data thus far presented demonstrate that patients with gastrointestinal cancer suf-

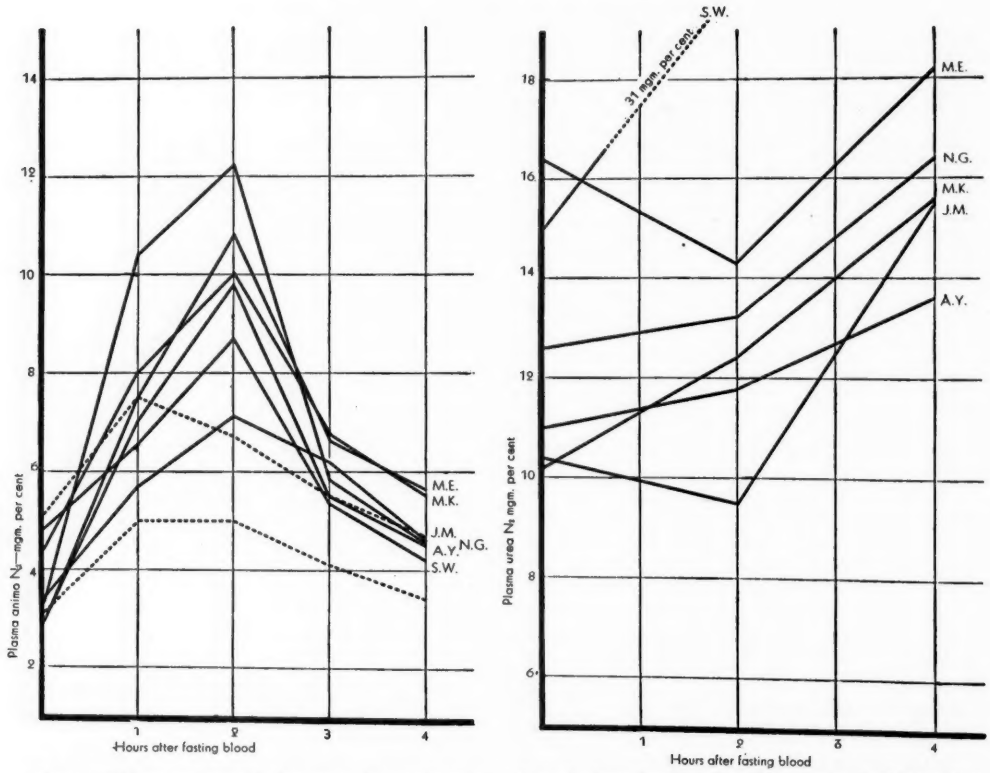

Chart 4. Plasma amino-acid nitrogen and urea nitrogen curves following the ingestion of 25 grams of glycine by 5 patients with gastric cancer and 1 patient with carcinoma of terminal esophagus. The area between the broken lines in the plasma amino-acid nitrogen chart represents the control levels. (Courtesy of *Annals of Surgery*–9.)

fer from a high incidence of hypoproteinemia which is not exclusively the result of dietary deficiency, repeated bleedings, hepatic dysfunction, or excessive catabolism of protein. Patients with benign organic lesions of the gastrointestinal tract have a markedly lower incidence and degree of hypoproteinemia, indicating that organic disease of the gastrointestinal tract per se is not the cause of the hypoproteinemia (Chart 9).

The preceding data warrant the hypothesis that the presence of the cancer in some manner acts as an agent preventing the normal fabrication of serum protein. This conclusion is substantiated by comparison of the serum proteins in patients with gastrointestinal cancer and those in whom the cancer had been removed from 2 months to 5 years previously. A significant increase in the plasma protein concentration of the patients whose cancer had been resected has been observed (Chart 8).

EFFECT OF SURGERY UPON PLASMA PROTEIN CONCENTRATIONS

Since patients with gastrointestinal cancer frequently undergo prolonged surgical procedures, and since serious postoperative complications result from the hypoproteinemic state a study was undertaken to ascertain whether or not (a) the serum protein levels in patients with gastrointestinal cancer fell after operation more frequently to lower levels than in other patients subjected to comparable surgical interventions, and (b) if so, was an increased protein catabolism responsible for this fact (5).

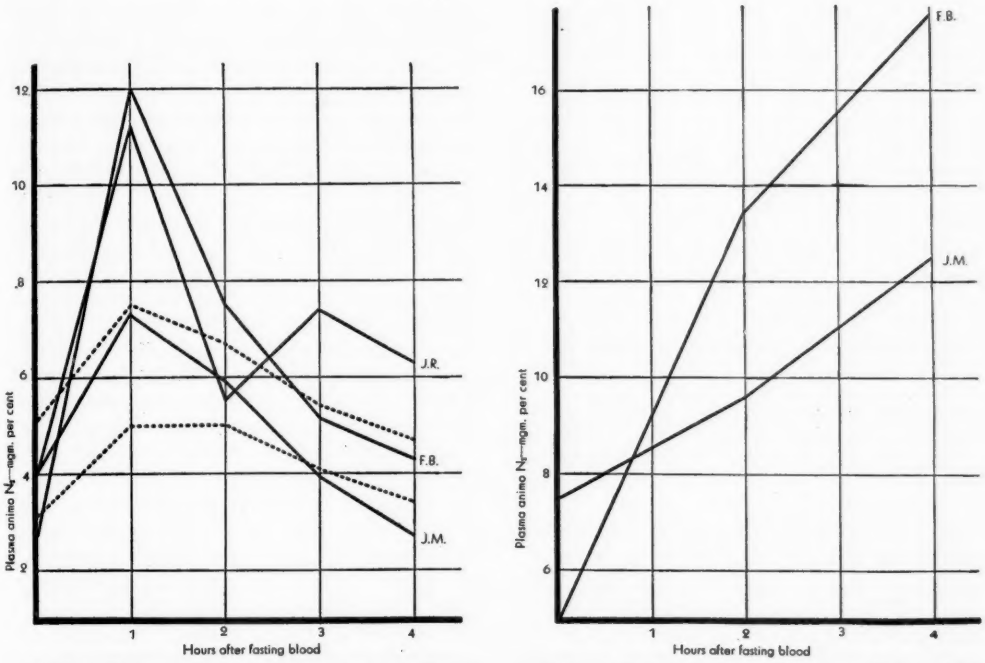

Chart 5. Plasma amino-acid nitrogen and urea nitrogen curves following the ingestion of 25 grams of glycine by 3 patients after a gastrectomy had been performed. The area between the broken lines in the plasma nitrogen chart represents the control levels. (Courtesy of *Annals of Surgery*–9.)

Three groups of patients were studied (Table I): Group I consisted of 47 patients with gastrointestinal cancer. Group II consisted of 9 patients with benign non-neoplastic diseases of the gastrointestinal tract. Group III consisted of 9 women with gynecological disorders.

The preoperative concentrations of serum protein in the 47 patients with gastrointestinal cancer of this series ranged from 4.6 to 7.5, and averaged 6.31 grams per cent. During the first 5 postoperative days 41 developed hypoproteinemia. The serum protein concentrations fell in 40 of the 47 patients studied. The average decrease in these instances was 0.81 and the range of decrease from 0.1 to 2.0 grams per cent. In the remaining 7 patients the serum protein concentrations after operation either remained constant or increased from 0.2 to 0.5 per cent.

During this 5 day postoperative period, the total urine was collected from 30 of the 47 patients studied. The average daily urinary nitrogen excreted by each of these individuals ranged from 6.0 to 16.8 grams and the average of the group was 8.96 grams per day. These values of nitrogen excreted indicate that probably from 187.5 to 525.0 grams of protein (average 280.0 gms. of protein) were catabolized by the patients with gastrointestinal cancer during the first 5 days after operation. Since these individuals had received during this same period only from 35 to 150 grams of protein (average 85 gm.), they apparently sustained after operation a significant amount of tissue breakdown. No correlation could be obtained between the decreased concentrations of serum protein and the amounts of nitrogen excreted by the patients of this group.

As control material for the observations just described, similar studies were made in 2 other groups of patients. The first of these consisted of 9 patients with non-neoplastic disorders

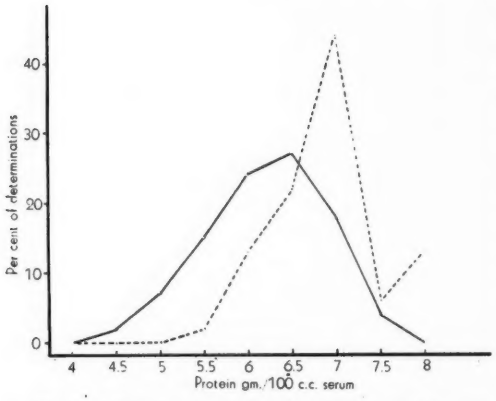

Chart 6. Frequency polygon of total serum protein concentration of patients with gastric cancer compared with patients with hepatic cirrhosis. —— gastric cancer; ---- hepatic cancer.

who were submitted to surgical procedures similar to those to which were subjected the patients with gastrointestinal cancer. The results obtained in the patients with non-neoplastic gastrointestinal disease form an interesting contrast to those of the patients with cancer.

The preoperative concentration of serum protein in the patients with benign gastrointestinal disease ranged from 5.9 to 7.1 grams, and averaged 6.54 grams per cent.

When these individuals were subjected to surgery their serum protein levels fell in 6 instances from 0.1 to 0.3 gram, average 0.18 gram per cent. In one, no change in the serum protein concentration was noted, and in the remainder these concentrations increased by from 0.1 to 0.4 gram per cent in that period. However, although no significant decrease in the concentrations of serum protein was observed in these individuals, nevertheless, they excreted from 5.3 to 13.8 grams of urinary nitrogen per day (average 8.90 grams per day) during the first five postoperative days. It is to be noted that these amounts of urinary nitrogen are the same as those excreted by the patients with gastrointestinal cancer who did develop hypoproteinemia. As in the latter group, no correlation could be made between the postoperative levels of serum protein and the amounts of urinary nitrogen excreted.

The second control group of patients investigated were 9 women subjected to gynecologic surgery. It was believed that this study would provide data of the effects on protein catabolism of intra-abdominal operations other than those on the gastrointestinal tract. The preoperative concentrations of serum protein of these 9 patients ranged from 5.9 to 7.6 grams, and averaged 6.61 grams per cent. Of these 4 had abnormally low levels. Within 5 days after operation the concentration of serum protein fell in 5 from 0.1 to 1.1 grams. The average decrease of these 5 patients was 0.38 gram per cent. The concentration of serum protein did not change in 1 instance, and increased from 0.1 to 0.2 gram per cent in the remaining 3 patients.

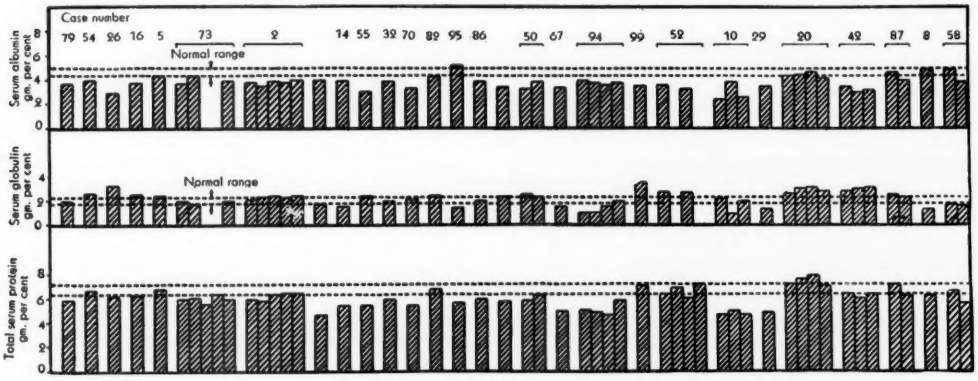
Case number
79 54 26 16 5 73 2 14 55 32 70 89 95 86 50 67 94 99 52 10 29 20 42 87 8 58
Normal range
Serum albumin gm. per cent
Normal range
Serum globulin gm. per cent
Total serum protein gm. per cent

Chart 7. The albumin and globulin concentrations in the serum of patients with gastric cancer.

During the first 5 postoperative days the average daily amounts of nitrogen excreted by the patients with gynecologic disorders ranged from 3.24 to 10.35 grams, and averaged 7.04 grams. As in the other 2 groups of patients who were studied, no correlation could be made between the amounts of urinary nitrogen which were excreted and the amounts by which the serum protein concentrations decreased.

It is of considerable importance to note, however, that although the 2 control groups of patients lost an average of 7.04 and 8.90 grams of urinary nitrogen per day, after operation the patients with gastrointestinal cancer excreted a comparable quantity of nitrogen, 8.96 grams per day. The average maximum change in the concentration of serum protein in the patients with gastrointestinal cancer, however, was 0.81 gram per cent, whereas the concentration of serum protein in the 2 control groups decreased only 0.18 and 0.38 gram per cent.

The maximum serum protein drop occurred on the fourth postoperative day. Despite rigorous attempts at re-establishing a normal plasma protein level, the plasma proteins remained low during the 29 day period following surgery that the patients were studied (Chart 10).

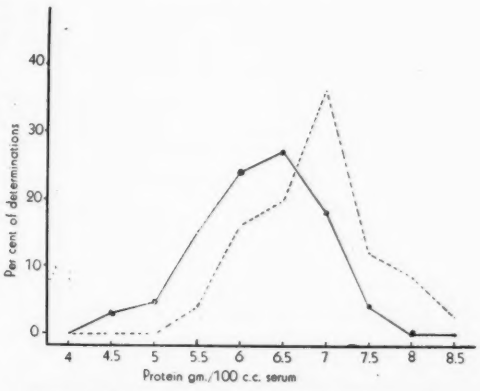

Chart 8. Frequency polygon of total serum protein concentration of patients with gastric cancer compared with a group of patients in whom the cancerous stomach previously had been resected. —— gastric cancer; ---- hepatic cancer.

The findings indicate that not only are the concentrations of serum protein in patients with gastrointestinal cancer low before operation, but those levels now have been found to fall to still further abnormally low limits after operation. There is now reason to believe that

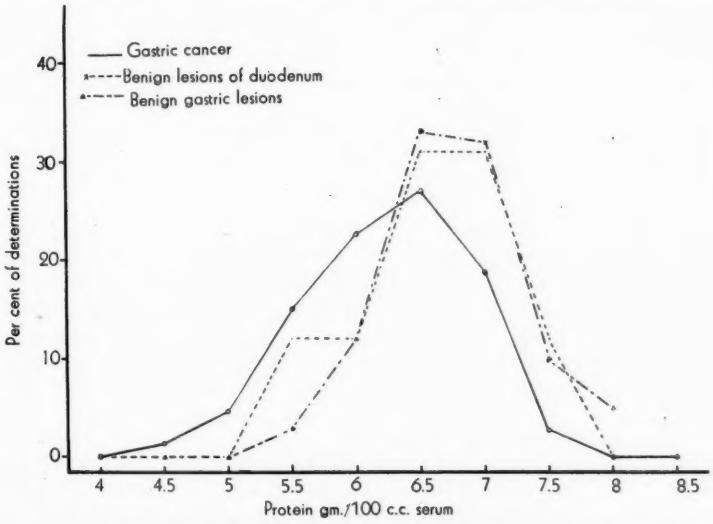

Chart 9. Frequency polygon of total serum protein concentration of patients with gastric lesions and of patients with benign duodenal lesions.

TABLE I.—EFFECT OF OPERATION UPON THE SERUM PROTEIN CONCENTRATION IN PATIENTS WITH DIFFERENT DISEASE PROCESSES AND THEIR EXCRETION OF URINARY NITROGEN

Patients with	Number of patients	Preoperative serum protein concentration gm. per cent	Average maximum drop in serum protein level during first 5 postoperative days—gm. per cent	Per cent of patients whose serum protein dropped after operation	Average daily urinary nitrogen during first 5 days postoperative gm.
Gastrointestinal cancer	47	6.31	0.81	84	8.96
Non-neoplastic disease of the gastrointestinal tract	9	6.54	0.18	67	8.90
Gynecologic disorder	9	6.61	0.38	55	7.04

the hypoproteinemic state developed after operation chiefly is responsible for the high incidence among these patients of wound disruption, disturbed electrolyte equilibrium (6), adynamic ileus, and gastrointestinal and peripheral edema. Because of the development of these serious postoperative complications the existence of hypoproteinemia in patients with gastrointestinal cancer becomes of considerable importance.

Although both the patients with gastrointestinal cancer and those of the 2 groups used as controls all excreted comparably equal amounts of urinary nitrogen after operation, only the first group of individuals sustained considerable reductions of their serum protein levels. The explanation for this observation probably is that (a) the tissue protein stores of patients with cancer of the gastrointestinal tract are depleted and, therefore, cannot restore the serum protein concentrations to their preoperative levels, and (b) the ability of these individuals to fabricate serum protein is impaired.

TABLE II.—THE CHEMICAL COMPOSITION OF LIVERS OF PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT

Patient	Histologic appearance of the liver	Glycogen, gm. per cent	Total lipid, gm. per cent	Total protein, gm. per cent	"Albumin" gm. per cent	"Globulin" gm. per cent	Serum protein gm. per cent
S.B.	Normal	1.3	12.5				
F.B.	Normal	3.6	22.0				
A.B.	Moderate fatty infiltration	1.9	24.0	14.7	3.9	10.8	6.6
H.D.	Normal	1.9	15.9	17.6	6.7	10.9	7.3
P.F.	Normal	1.0	14.8	17.2	5.1	12.1	7.2
T.G.	Normal	1.45	12.1	15.9	5.8	10.1	6.8
S.H.	Normal	1.8	5.3				
A.H.	Normal	2.2	13.0				
W.J.	Normal	2.7	8.55	15.8	5.5	10.3	5.7
M.P.	Normal	1.4	27.1	16.0	8.05	7.97	5.7
L.R.	Normal	4.0	9.5	17.95	4.6	13.35	7.1
L.S.	Normal	2.0	6.9	16.2	5.8	10.4	4.2
J.S.	Normal	5.8	24.1				
J.T.	Normal	8.3	14.8	17.8	3.2	14.6	6.7
J.T.	Moderate fatty infiltration	2.4	29.0				
V.T.	Normal	1.3	22.4	12.9	4.4	8.5	7.4
S.W.	Normal	2.1	35.0	16.8	4.3	12.5	4.6
E.Y.	Normal	7.3	16.9	15.2	4.1	11.1	6.2
Average		2.91	17.43	16.17	5.10	11.05	

(Courtesy of *Annals of Internal Medicine*—7).

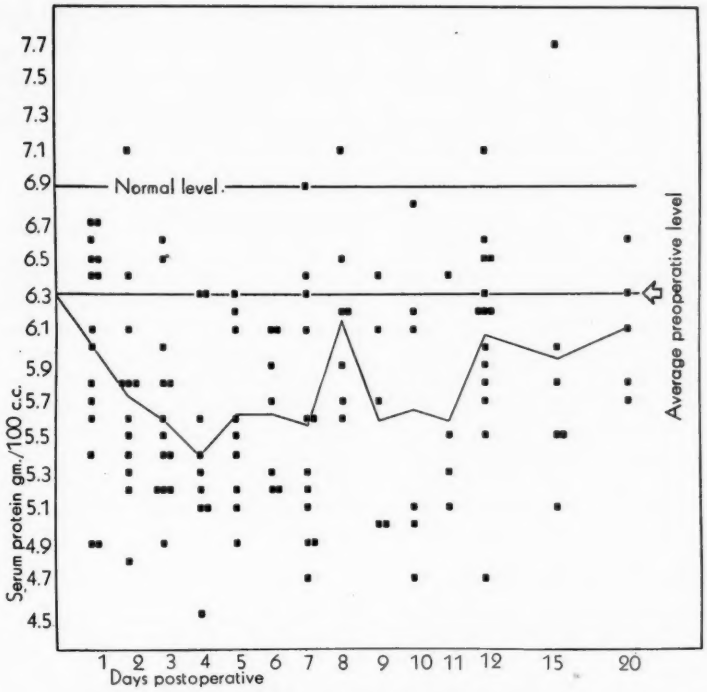

Chart 10. Postoperative serum protein alterations in patients with gastric cancer. The small black squares represent individual determinations. The curve demonstrates the average daily postoperative fluctuation of the serum protein concentration.

RELATIONSHIP OF LIVER PROTEIN TO PLASMA PROTEIN CONCENTRATION

From evidence recently presented, a decreased concentration of serum protein has been found associated with depletion of tissue proteins (12).

It has been observed that the livers of fasted animals are depleted of proteins with great rapidity (4), and that when animals are maintained on high protein diets all the protein fractions of their livers increase (11). These observatious suggest that the liver may store proteins, and that those stores might be abnormally reduced in the hypoproteinemic patients.

To note if any correlation existed between the protein concentration of the liver and the depleted plasma protein content, chemical analyses of the livers of 12 patients with gastrointestinal cancer were performed. The data are summarized in Table II.

The concentrations of proteins in the normal human liver are not known and so not available for purposes of comparison. One may hazard, perhaps, a comparison of the values obtained with those of animal liver tissue. The total protein in the liver of the rat has been found to average 15.5 grams, the "albumin" 2.1 grams, and the "globulin" 13.4 grams per cent. In the dog liver the average total protein content has been found to be 17.5 grams per cent.

The total hepatic protein in 12 patients with gastrointestinal cancer ranged from 12.9 to 17.95 and averaged 16.17 grams per cent. The "albumin" contents averaged 5.10 grams and varied from 3.2 to 8.05 grams per cent, and the "globulin" averaged 11.0 and ranged

TABLE III.—EFFECTS OF INGESTED PROTEIN AND AMINO ACIDS ON CHEMICAL COMPOSITION OF LIVERS OF PATIENTS WITH GASTROINTESTINAL CANCER

Dietary supplement	No. of patients	Hepatic concentration of lipid		Hepatic concentration of glycogen	
		Range, gm. %	Average, gm. %	Range, gm. %	Average, gm. %
None	28	5.3—35.0	16.40	0.5—8.3	2.56
High protein (2.5 gm./kgm./day)	7	4.6—7.55	5.59	0.8—3.8	2.23
Amino acids (75 gm.)	9	9.05—26.2	15.45	1.3—3.3	2.39

(Courtesy of the Society for Experimental Biology and Medicine—1)

from 8.5 to 14.6 grams per cent. No apparent correlation was found between the concentrations of protein in the serum and in the livers of the patients studied.

It is interesting to note that the liver apparently does not contain large stores of "albumin." Assuming an average liver weight of 1,500 grams, the average concentration of 5.1 grams per cent obtained from hepatic "albumin" would amount only to 76.5 grams of protein, or about one-quarter that of the normal circulating serum albumin. Thus, if the "albumins" of the liver are similar to those of the serum, or are converted readily into that fraction, the store they constitute for serum albumin replacement is a small one.

Furthermore, the administration of proteins to patients preoperatively does not affect the hepatic protein concentration. It does, however, exert a pronounced lipotropic effect in significantly reducing the fat content of the liver (Table III) (1).

TABLE IV.—THE EFFECT OF GASTRIC SURGERY UPON THE CHEMICAL COMPOSITION OF THE LIVER

Patient	Diagnosis	Operation	Protein gm. per cent			Albumin gm. per cent			Globulin gm. per cent		
			Pre-operative	Post-operative	Difference	Pre-operative	Post-operative	Difference	Pre-operative	Post-operative	Difference
A.B.	Adenoma malignum (Grade II) of stomach	Subtotal gastrectomy	14.7	14.0	−0.7	3.92	2.91	−1.01	10.80	11.11	+0.31
O.B.	Adenocarcinoma (Grade IV) of stomach	Subtotal gastrectomy	15.10	16.80	+1.70	7.04	7.72	+0.68	8.06	9.08	+1.02
C.C.	Adenocarcinoma (Grade IV) of stomach	Subtotal gastrectomy	15.90	15.00	−0.90	6.12	7.48	+1.36	9.78	8.52	−1.26
F.G.	Adenocarcinoma (Grade III) of stomach	Subtotal gastrectomy	17.90	16.75	−1.15	4.15	4.96	+0.81	13.75	11.79	−1.96
L.S.	Carcinoma of stomach	Total gastrectomy	16.2	17.0	+0.8	5.77	....	....	10.43	....	....
I.T.	Carcinoma of stomach	Subtotal gastrectomy	17.80	16.60	−1.20	3.18	4.55	+1.37	14.6	12.0	−2.6
B.V.	Adenocarcinoma (Grade IV) of stomach	Subtotal gastrectomy	11.90	11.07	−0.83	3.16	3.44	+0.28	8.74	7.63	−1.11
J.H.	Gastric polypi	Subtotal gastrectomy	15.8	15.8	0.	4.37	4.37	0.	11.45	11.45	0.
F.H.	Duodenal ulcer	Gastro-enterostomy	14.3	12.6	−1.7	1.46	2.54	+1.08	12.94	10.08	−2.86
J.R.	Boeck's sarcoid of stomach and liver	Subtotal gastrectomy	13.1	14.1	+1.0	4.22	6.35	+2.13	8.83	8.44	−0.39
J.S.	Gastritis	Subtotal gastrectomy	11.4	12.3	+0.9	2.46	4.57	+2.11	8.94	8.70	−0.24
Averages			14.65	14.80	−1.89	4.21	4.88	+0.88	10.42	9.88	−0.9

(Courtesy of *Annals of Surgery*—10).

The fact that the liver proteins are not static units but are dynamically changing is evidenced by the analyses of livers of 11 patients before and after surgical intervention. All patients received spinal anesthesia and were given an average of 500 cubic centimeters whole blood and 500 cubic centimeters of normal saline during the operation (Table IV).

During the course of the operation, an increase in the albumin fraction in the postoperative specimens occurred in 8 instances, and a decrease occurred in 2. In one there was no change. The average change of all determinations was an increase of 0.88 gram per cent.

The increased albumin was usually associated with a decrease of globulin content. There was an average loss of 0.9 gram per cent. These alterations demonstrate a change of the protein fractions during operative stress. The physiological implication of this alteration is not apparent (10).

These experiments indicate that no apparent correlation exists between the liver protein concentration and the concentration of serum protein. The stress of surgery does induce certain alterations in liver proteins, the nature of which is not known. The liver cannot be considered a protein storehouse to supply plasma protein during surgical stress.

SUMMARY AND CONCLUSIONS

1. The data herein presented demonstrate that patients with gastrointestinal cancer suffer from a significant degree of hypoproteinemia on admission to the hospital. The hypoproteinemia is not exclusively the result of dietary deficiency, excessive bleeding, or excessive catabolism, but appears to be the result of a defect in protein synthesis.

2. One of these abnormalities consisted in the inability of the patients with gastrointestinal cancer properly to absorb, assimilate, and metabolize the amino acid glycine.

3. Following resection of the cancer, the fact that the serum protein levels returned to normal suggests that the presence of the cancer acts as an insulting agent inhibiting normal plasma protein regeneration.

4. The fact that the postoperative course in patients with gastrointestinal cancer is associated with a pronounced drop in plasma protein concentration and various clinical complications resulting from this hypoproteinemia, focuses attention on the need for prolonged and careful preoperative regimens to maintain normal nitrogen equilibrium.

5. The chemical analyses of the liver revealed that the liver is not a storehouse for significant quantities of albumin, and that there is marked fluctuation in the protein content of the liver in the course of an intra-abdominal operation.

6. During the first 5 postoperative days the urinary nitrogen in patients with gastrointestinal cancer averages the same as in patients with gynecological disorders and those with benign gastrointestinal tract disease, but in the latter 2 groups of patients the postoperative course is not frequently associated with a significant incidence or degree of hypoproteinemia.

7. These data suggest that patients with gastrointestinal cancer may suffer from a deprivation of the tissue protein, hence are not able to compensate for the nitrogen debt which develops during the postoperative course.

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THE USE OF BETA-METHYLCHOLINE URETHANE IN POSTOPERATIVE URINARY RETENTION

FRED K. GARVEY, M.D., F.A.C.S., MEDFORD C. BOWMAN, M.D., and WILLIAM L. ALSOBROOK, M.D., Winston-Salem, North Carolina

CONSIDERABLE search has been made for an effective drug to use for the treatment of postoperative urinary retention. Time honored methods are unreliable and most of the drugs which have been used have proved inadequate. We have found beta-methylcholine urethane beneficial in a large percentage of these cases although it is not a final solution to the problem.

Postoperative urinary retention is that condition occurring following an operation in which the patient cannot void despite a full bladder, normal kidney function, and the absence of any organic obstruction. Normally the urinary bladder fills passively and empties under voluntary control. It is partly under voluntary control and is richly supplied by three sets of nerves. The sympathetic nerve supply is through the presacral and hypogastric nerves, the stimulation of which relaxes the bladder wall and contracts the internal sphincter. The parasympathetic nerve supply is by way of the nervi erigentes, upon stimulation of which relaxation of the external sphincter and contraction of the detrusor result. The pudendal nerve produces voluntary control of the external sphincter muscle and other perineal accessory muscles of urination. The desire to void depends upon intravesical pressure and not necessarily on the amount of urine present in the bladder. The average male bladder capacity is about 300 cubic centimeters and the female bladder capacity slightly less. The desire to void arises with a urinary bladder volume of 230 to 250 cubic centimeters. Contraction of the detrusor muscle, which constitutes the entire bladder musculature, and the relaxation of the sphincters bring about emptying of the bladder. The trigonal muscle shortens and helps open the sphincters.

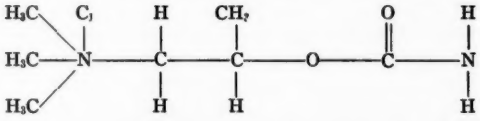
From the Departments of Urology and Surgery, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina.

MATERIAL AND METHODS

Since the pioneer work of Dale, in 1914, it has been known that drugs belonging to the choline series mimic the effects produced by stimulation of the parasympathetic nervous system. Dale introduced the term "parasympathomimetic" to describe these properties of choline derivatives. It has also been observed that atropine annuls the parasympathetic effects of choline derivatives (10).

Acetyl-beta-methylcholine (mecholyl) (2, 3, 4, 7) and carbaminoyl-choline (doryl) (6, 9) have been the most widely used choline derivatives for their effects on the urinary bladder. Mecholyl is not stable and is quickly destroyed by the body fluids. Doryl has been found to be stable but possesses a very strong nicotinic action. We have had relatively little clinical experience with either of these drugs.

Carbaminoyl-beta-methylcholine chloride (beta-methylcholine urethane) was synthesized by Major in 1935 at the suggestion of Simonart (8). The empirical formula is $C_7H_{17}N_2O_2C_1$ and the structural formula is:



The pertinent quantitative solubilities are 1 gram in 0.6 cubic centimeter of water at room temperature and 1 gram in 12.5 cubic centimeters of 95 per cent ethanol at room temperature. The aqueous solution is very stable. The therapeutic and toxic effects of this drug are considerably less than those with doryl. This drug at present appears to be the most promising of the choline derivatives in the treatment of functional urinary retention.

TABLE I.—RESULTS OF SUBCUTANEOUS ADMINISTRATION OF BETA-METHYLCHOLINE URETHANE IN POSTOPERATIVE URINARY RETENTION

Type of operation	Cases	Success	Partial success	Failure
Colporrhaphy	8	2	5	1
Hemorrhoidectomy	11	7	2	2
Pelvic celiotomy	3	3	0	0
Upper abdominal celiotomy	4	1	1	2
Herniorrhaphy	10	7	2	1
Abdominoperineal resection	1		1	
Upper urinary tract procedures	5	3	2	
Lobectomy and pneumonectomy	4	3	1	
Laminectomy, air myelogram, and craniotomy	9	8		1
Cystoscopy	6	3	2	1
Appendectomy	15	9	3	3
Totals	76	46 (60%)	19 (25%)	11 (15%)
Male	43	31 (72%)	7 (16%)	5 (12%)
Female	33	15 (46%)	12 (37%)	6 (17%)

The ability to control fully the side effects of beta-methylcholine urethane by the administration of atropine (5) makes it a more desirable drug than other choline esters. Starr and Ferguson (11) have given very complete data concerning the drug and its action in various normal and abnormal conditions.

The drug was given orally to the first group of patients in doses ranging from 4 milligrams every 4 hours up to 10 milligrams every 30 minutes for three doses as indicated by individual response. The results were poor and have not been included in this report. Subcutaneous administration has been much more effective and the drug is now given exclusively by this route. The most efficient results are obtained by giving 5 milligram doses at 30 minute intervals for three injections. If the patient voids satisfactorily after any one of the three administrations, the drug is discontinued. The patient is catheterized if the third 5 milligram dose does not produce urination and then the drug is repeated as indicated later. We observed each case of the recorded group continuously throughout each procedure. The drug is probably too potent for safe administration by the intravenous or intramuscular route in the treatment of postoperative urinary retention.

RESULTS

We have recorded the results obtained in 76 consecutive unselected cases of postoperative urinary retention in which the drug was administered subcutaneously as outlined herein. Other methods of treatment had been tried without success in all except 12 patients and the time interval following the operative procedure varied from 6 hours to the eighth postoperative day. Dosages as large as 10 milligrams every 30 minutes for three injections were given subcutaneously in some of the earlier patients, but in some instances the side actions of the drug were rather uncomfortable and the clinical results were only slightly more favorable. Since accumulating the data recorded in Tables I, II, and III, we have administered the drug in about 150 additional cases with comparable results. There are 43 male and 33 female patients in the detailed recorded groups.

Tables I and II list the patients as to the type of operative procedure performed previous to the complication of postoperative retention and group the cases in three categories according to the results. These latter include successes, partial successes, and failures.

None of the patients classified as the successful group had to be catheterized. Forty-six patients voided spontaneously after subcutaneous administration of 5 milligrams of beta-methylcholine urethane repeated at 30 minute intervals for three times when necessary. Seventeen of the 46 patients voided after being given 5 milligrams of the drug and in the remaining 29 it had to be repeated once or twice. The drug was routinely repeated if the bladder could be percussed or if the patient remained uncomfortable because of bladder distention following the first or second dose. The number of successes was higher in the male group.

In the patients classified as partially successful, one series of beta-methylcholine urethane was given as outlined previously and the individual did not void. The patient was then catheterized. Eight to 10 hours later the pro-

TABLE II.—PROCEDURES RESULTING IN VOIDING FOLLOWING THE SUBCUTANEOUS ADMINISTRATION OF BETA-METHYLCHOLINE URETHANE IN 76 CASES OF POSTOPERATIVE URINARY RETENTION

Procedure	No. of cases voiding	No. of cases not voiding	Per cent	Classification
A. Single 5 mgm. dose	17		22%	
B. Two or three 5 mgm. doses at 30 minute intervals	29		38%	
Total	46		60%	Successes
C. Three 5 mgm. doses at 30 minute intervals, followed by catheterization; drug repeated if necessary	12		16%	
D. Procedure C repeated once	7		9%	
Total	19		25%	Partial successes
E. Failure of the above procedures and some supplementary method used		11	15%	Failures

TABLE III.—ACTIONS AND SIDE ACTIONS OF BETA-METHYLCHOLINE URETHANE

	No.	Per cent
A. Circulatory		
Flush	62	80
Sweating	62	80
Fall in blood pressure	24	30
Weakness	18	25
Pulse change	None had any significant change	
B. Urinary		
Bladder and/or urethral pain	70	92
C. Gastrointestinal		
Increased peristalsis	38	50
Flatus	26	35
Nausea	14	20
Nausea and vomiting	12	15
Defecation	8	10
Epigastric discomfort	4	5
D. Secretory		
Salivation	22	30
Lacrimation	8	10
E. Respiratory		
Bronchoconstriction	8	10
F. Visual		
Miosis	2	3
No action	12	16

cedure was repeated if the patient was uncomfortable or if he desired to void and could not. The partial success cases are classified arbitrarily as those in which the drug-catheterization therapy was instituted one and two times. A total of 19 cases make up this group. Twelve of the 19 patients were catheterized once and 7 were catheterized twice and the drug was given as indicated.

Eleven patients in which the beta-methylcholine urethane-catheterization procedure was repeated more than twice and in which some other method of treatment was started are classified as failures. We have also included in this group of 11 cases 4 patients who because of uncomfortable side actions of the drug preferred catheterization or some other mode of treatment to further administration of the drug.

The actions and side actions of beta-methylcholine urethane as we observed them are summarized in Table III. These are listed under six general headings—circulatory, urinary, gastrointestinal, glandular (secretory), respiratory, and visual. Doses of 5 milligrams each repeated at 30 minute intervals as outlined previously did not cause any of the patients to have any alarming side effects although a few did become rather uncomfortable after the second or third dose. It was not necessary to give atropine to any of this group of patients to relieve the side actions but we did give 0.9 milligram (1/75 gr.) subcutaneously to each of 10 patients to observe its effect and found that the parasympathetic actions of beta-methylcholine urethane were relieved completely in 10 to 15 minutes by the atropine. Atropine was occasionally given to apprehensive patients when larger doses than 5 milligrams of urethane were administered and in no case did atropine fail to counteract the side actions completely. Flushing (80%), sweating (80%), and bladder pain, urethral pain or both (92%) were the effects most frequently encountered and they usually occurred in this sequence. All patients who voided successfully following administration of the drug had bladder pain, urethral pain or both. The symptoms of respiratory and visual side effects were usually elicited only on direct questioning of the patient. There was no significant change in the pulse rate and the systolic blood pressure did not fall more than 8 points in any patient. The drug proved to be a useful adjunct to the treatment of postoperative intestinal distention in 26 (35%) patients who passed flatus following the administration of the drug.

DISCUSSION

It is, of course, difficult to evaluate accurately the effectiveness of any drug or procedure in the treatment of postoperative urinary retention, for psychogenic factors play a large role in the problem. It has been repeatedly observed that functional retention is seldom seen in the postoperative mentally deficient patient. The value of beta-methylcholine urethane is exhibited in its minimal toxic side reactions and in the fact that atropine will completely neutralize these side actions should they become excessive.

We have previously outlined what we consider the most effective method and drug dosages. The patient, if female, should be placed on a bedpan at the time of each administration or very shortly afterward. With male patients a urinal should be immediately available at the time of drug administration. The drug is usually effective in 5 to 15 minutes. It is probably more effective in male patients because of the greater simplicity of the urinal over the bedpan in voiding. The drug is given preferably on an empty stomach, before meals and more than 2 hours after eating or taking fluids orally. If the drug is given immediately after eating about one-third of the patients will develop nausea and vomiting. Beta-methylcholine urethane seldom has to be repeated more than two or three times after the patient has voided one time and once it has been successful in emptying the bladder it is practically always successful on subsequent administration. We have observed no local reactions when the drug is given subcutaneously. One 5 milligram dose was inadvertently given intramuscularly. The patient urinated 700 cubic centimeters within less than 4 minutes and had rather accentuated and distressing side actions but these were relieved within 10 minutes by the prompt administration of 1/75 grain (0.9 mgm.) of atropine subcutaneously. Better results are obtained if the drug is not given to apprehensive patients. We personally administered the drug and observed all the patients in the present group but in later cases left the administration to the supervising nurse, each dose being ordered separately and the procedure varied according to the effect of the preceding dose. The side actions, if present, are usually more pronounced with the first series and decrease with each succeeding series. Adequate fluid intake is of great importance especially after the drug has been effective one time. The drug was found to be very effective in cases in which the patient was having urinary overflow or voiding small amounts spontaneously. The type of anesthetic agent used for the operative procedure apparently had little effect on the results obtained.

The mechanical effects of the operative procedure doubtless affect the results to be expected from any parasympathomimetic drug used in the treatment of functional postoperative urinary retention. Abdominal operations affect the action of the abdominal musculature used in aiding the voiding act. Our highest incidence of partial successes was in the group of patients who had anterior colporrhaphy, in which there was trauma and probably actual constriction of the tissues surrounding the urethra. The drug cannot be expected to act as successfully in the case of patients in whom part of the nerve supply to the urinary bladder is destroyed.

Beta-methylcholine urethane is contraindicated in the presence of vesical neck obstruction, asthma, and hyperthyroid conditions. It would not seem wise to use it in patients after recent intestinal anastomoses, obstructive resections or other intestinal procedures where increased peristalsis might prove harmful. It should not be used in patients with coronary sclerosis, known heart disease, or in elderly individuals in whom tachycardia and a drop in blood pressure might lead to myocardial damage or infarction.

SUMMARY AND CONCLUSIONS

1. Beta-methylcholine urethane, a choline derivative, has been used in the treatment of 76 consecutive unselected cases of postoperative functional urinary retention.

2. The drug is stable, shows minimal side actions, and these can be completely counteracted by the use of atropine.

3. The drug was successful in relieving the urinary retention in 46 (60%) of the cases and partially successful in 19 (25%). Eleven (15%) cases were classified as failures.

4. The contraindications to the use of the drug for postoperative retention are vesical neck obstructions, asthma, hyperthyroidism, recent intestinal anastomoses, elderly individuals except cautiously in small doses and in individuals with coronary sclerosis or known heart disease.

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THE EFFECT OF SULFATHALIDINE ON THE BLEEDING AND CLOTTING TIME OF THE BLOOD AND PROLONGATION REDUCTION BY THE ADMINISTRATION OF VITAMIN K

LOUIS T. WRIGHT, M.D., F.A.C.S., FRANK R. COLE, M.D., and LYNDON M. HILL, Jr., M.D., New York, New York

SULFATHALIDINE or phthalylsulfathiazole was introduced in 1943 by Poth and Ross (11). The antibacterial action of this compound effects a considerable reduction of the gram negative bacteria of the bowel, both anaerobic and aerobic organisms being susceptible. Sulfathalidine has from two to four times greater bacteriostatic activity than succinylsulfathiazole as indicated by the effect on coliform organisms.

Allen found that increased bleeding had occurred after 4 or 5 days of sulfasuxidine administration in one-fifth of the patients with a carcinoma of the colon. Poth (8,9,10) observed an increase of bleeding in an occasional patient but stated that when sulfasuxidine was used the incidence of bleeding was not high.

Firor reported that in 2 patients with large ulcerating carcinomas of the colon, the administration of succinylsulfathiazole had to be discontinued because of alarming hemorrhage. Sanders and Halperin reported postoperative hemorrhages accompanied by a low prothrombin level in 2 patients following the use of sulfasuxidine, and in both cases vitamin K intravenously administered stopped the hemorrhage. In both of these cases, the prothrombin level had been normal prior to the administration of sulfasuxidine. They believed that the marked reduction of vitamin K synthesizing colonic bacteria brought about by sulfasuxidine was partly responsible for the hemorrhagic phenomenon. They stated that since then they have routinely given synthetic vitamin K by mouth to all patients receiving sulfasuxidine.

Kornberg and Seberell studied the production of vitamin K deficiency in rats with sulfapyrazine, sulfadiazine, sulfathiazole, sulfaguanidine, and succinylsulfathiazole, and they found all of these drugs effective in varying degrees in producing rapidly and consistently a severe vitamin K deficiency with a significant prolongation of the clotting time of whole blood and with massive hemorrhages. They found that the order of effectiveness of the sulfonamide compounds used in the production of vitamin K deficiency was in direct proportion to their effectiveness in regard to bacteriostasis of coliform organisms in the intestines of the animals.

In man, bacteria, one natural source of vitamin K, are of great practical importance. Almquist has reported that cultures of numerous organisms such as Staphylococcus aureus, Escherichia coli, Bacillus subtilis are all rich in vitamin K. The large amount of vitamin K formed and constantly absorbed by coliform organisms in the human bowel probably explained the difficulty with which hemorrhagic disease is produced in mammals by feeding a vitamin K deficient diet and the rarity with which simple nutritional deficiency of vitamin K is observed in man, as shown by Kark and Lozner. Kolmer states that hypoprothrombinemia may be caused by actual lack of vitamin K due to temporary sterility of the intestinal tract.

With these facts in mind and because clinically we have observed increased bleeding with the use of sulfathalidine, although Poth (8,9,10) and Allen have reported no increase, we decided to observe the bleeding and clotting times of all patients receiving sulfathalidine. Poth has reported bleeding and clotting times to be normal when sulfathalidine was used. We determined the bleeding and clotting time of patients before sulfathalidine therapy

From the Surgical Service of Harlem Hospital.

TABLE I.—BLEEDING AND CLOTTING TIME AFTER 5 DAYS' ADMINISTRATION OF SULFATHALIDINE

Case No.	Diagnosis	Red blood count	White blood count	Bleeding time		Coagulation time	
				Min.	Sec.	Min.	Sec.
1	Intestinal obstruction	3,750,000	12,600	1	0	3	30
		4,200,000	10,400	2	0	3	0
2	Rectal stricture, lymphogranuloma venereum	3,500,000	9,200	2	0	5	0
		3,900,000	8,400	2	30	4	0
3	Rectal stricture, lymphogranuloma venereum	3,600,000	7,400	0	45	2	45
		3,800,000	6,000	2	0	3	0
				2	0	4	0
4	Fistula in ano	4,200,000	8,400	2	0	0	45
		4,000,000	10,400	2	30	5	0
5	Pelvic inflammatory disease	3,800,000	6,400	0	35	2	30
		3,800,000	7,200	2	0	4	0
6	Carcinoma of anus	2,600,000	10,500	1	30	5	0
		3,500,000	7,600	2	30	7	0
7	Stab wound of splenic flexure of colon	—	—	1	30	5	0
				1	30	4	0
				3	12	9	30
8	Fistula in ano	4,400,000	12,100	1	30	3	30
		4,600,000	7,800	3	0	7	0
9	Carcinoma of splenic flexure	3,400,000	7,800	2	0	4	0
		3,600,000	6,100	3	0	4	0
				2	12	6	24
10	Gastroenteritis	4,800,000	8,800	2	30	4	30
				3	0	3	0
11	Carcinoma of rectum	3,400,000	9,800	1	30	4	0
		3,700,000	6,400	4	0	7	0
				2	30	7	30
12	Gangrenous small intestine	3,400,000	14,200	1	30	3	0
		4,000,000	8,600	3	30	5	15
				5	0	8	6
13	Stab wound of splenic flexure	3,400,000	10,600	1	30	4	0
		3,600,000	7,800	2	30	5	6
				1	6	6	0
14	Appendicitis	4,800,000	12,600	1	0	3	0
				2	0	7	0
15	Pilonidal cyst	—	—	1	30	2	30
				2	18	8	0
16	Hemorrhoidectomy	4,200,000	6,400	0	45	2	30
		4,200,000	7,800	2	30	8	0
17	Pelvic inflammatory disease	4,600,000	7,100	1	0	2	30
		3,800,000	6,400	2	18	6	18
18	Carcinoma of rectum	3,400,000	6,200	0	45	2	0
		3,000,000	5,400	2	27	6	0

TABLE I.—BLEEDING AND CLOTTING TIME AFTER 5 DAYS' ADMINISTRATION OF SULFATHALIDINE—Continued

Case No.	Diagnosis	Red blood count	White blood count	Bleeding time		Coagulation time	
				Min.	Sec.	Min.	Sec.
19	Carcinoma of stomach	2,850,000	8,400	1	0	3	0
		2,750,000	5,200	2	0	11	0
20	Carcinoma of rectum	2,700,000	9,200	0	45	1	30
		3,400,000	6,100	2	0	8	0
21	Intestinal obstruction	4,100,000	6,400	1	30	2	6
		4,200,000	5,200	3	0	7	0
22	Peptic ulcer	3,200,000	6,100	1	0	2	0
		4,400,000	7,800	1	30	4	30
23	Peptic ulcer	3,700,000	11,200	1	6	2	30
		3,850,000	5,200	2	0	5	0
24	Intestinal obstruction	4,100,000	12,100	1	6	3	0
		3,900,000	5,400	1	0	4	0
25	Intestinal obstruction	4,200,000	12,500	1	30	4	15
				2	45	6	20
26	Acute appendicitis	4,500,000	15,000	2	15	5	36
				4	20	6	40
27	Acute appendicitis	4,300,000	14,500	1	45	4	20
				2	55	6	30
28	Acute gastroenteritis	4,600,000	7,000	2	35	4	15
				2	30	4	20
29	Rectal stricture, lymphogranuloma venereum	3,800,000	6,500	2	35	4	17
				4	45	7	15
30	Penetrating stab wound of ileum	3,900,000	8,500	1	47	3	55
				1	40	3	55
31	Rectal stricture, lymphogranuloma venereum	3,750,000	7,200	2	10	4	15
				2	15	4	40
32	Intestinal obstruction	4,250,000	11,500	1	45	3	50
				1	40	4	0
33	Acute appendicitis	4,350,000	15,500	2	20	3	10
				4	25	6	15
34	Rectal stricture, lymphogranuloma venereum	3,650,000	12,500	3	10	4	40
				4	15	6	45
35	Carcinoma of rectum	3,400,000	9,500	2	40	4	30
				4	15	7	25
36	Intestinal obstruction	3,900,000	13,500	1	55	3	40
				2	10	4	10
37	Carcinoma of splenic flexure	3,300,000	8,200	1	50	5	20
				4	50	7	30
38	Stab wound of transverse colon	4,300,000	7,500	1	35	3	20
				3	40	6	40
39	Intestinal obstruction	4,200,000	12,200	1	55	3	45
				3	10	6	55

TABLE I.—BLEEDING AND CLOTTING TIME AFTER 5 DAYS' ADMINISTRATION OF SULFATHALIDINE—Continued

Case No.	Diagnosis	Red blood count	White blood count	Bleeding time		Coagulation time	
				Min.	Sec.	Min.	Sec.
40	Intestinal obstruction	4,600,000	11,500	2	10	4	5
				2	0	4	30
41	Intestinal obstruction	3,900,000	14,500	1	46	3	25
				3	12	5	40
42	Gunshot wound of ileum and large bowel perforation	4,100,000	9,200	1	32	2	10
				1	45	2	30
43	Stab wound of transverse colon	3,750,000	8,200	1	25	2	50
				3	20	5	10
44	Gangrenous appendicitis	3,950,000	15,200	1	10	3	30
				1	15	3	10
45	Gangrenous appendicitis	4,600,000	14,300	2	0	2	45
				3	15	5	10
46	Gunshot wound of transverse colon	4,250,000	9,300	1	30	3	0
				5	10	8	10
47	Rectal stricture, lymphogranuloma venereum	3,650,000	11,500	1	10	2	30
				3	45	7	20
48	Ischiorectal abscess	3,950,000	15,200	2	20	3	0
				3	0	3	15
49	Multiple fistulae in ano	3,750,000	14,500	1	45	2	30
				4	50	8	0
50	Perirectal abscess	3,800,000	12,200	1	0	2	0
				1	15	2	30
51	Intestinal obstruction	3,700,000	9,800	1	45	2	15
				3	45	6	30
52	Gastroenteritis with severe diarrhea	4,400,000	14,800	2	0	3	45
				4	15	7	30
53	Rectal stricture, lymphogranuloma venereum	3,650,000	7,600	1	30	2	15
				4	30	7	45
54	Gangrenous appendicitis	4,350,000	16,800	2	15	1	45
				4	45	6	30
55	Gastroenteritis with diarrhea	4,400,000	12,700	1	45	2	30
				2	0	3	0
56	Ischiorectal abscess	3,950,000	13,400	1	30	2	0
				3	45	6	30
57	Acute appendicitis	4,350,000	14,500	1	50	3	15
				1	45	3	5
58	Rectal stricture, lymphogranuloma venereum	3,300,000	7,600	1	15	3	45
				3	15	6	50
59	Fistula in ano	4,100,000	8,200	1	15	3	10
				3	20	6	10
60	Melanoblastoma of the rectum	3,600,000	9,100	1	45	4	15
				3	20	6	45

TABLE I.—BLEEDING AND CLOTTING TIME AFTER 5 DAYS' ADMINISTRATION OF SULFATHALIDINE—Continued

Case No.	Diagnosis	Red blood count	White blood count	Bleeding time		Coagulation time	
				Min.	Sec.	Min.	Sec.
61	Intestinal obstruction	4,100,000	10,500	1	20	3	10
				3	30	7	15
62	Stab wound of hepatic flexure	3,750,000	8,600	1	45	3	40
				3	20	7	15
63	Acute appendicitis	4,200,000	13,250	1	15	3	10
				2	10	3	45
64	Rectal abscess	3,800,000	14,500	1	25	2	10
				3	50	6	55
65	Carcinoma of rectum	3,300,000	5,600	1	10	4	10
				3	20	6	55
66	Fistula in ano	4,100,000	8,450	1	50	3	15
				3	10	6	25
67	Stab wound in transverse colon and stomach	3,550,000	9,200	1	45	3	5
				1	50	3	20
68	Acute gastroenteritis	4,300,000	10,500	1	50	3	40
				2	5	4	10
69	Acute appendicitis	4,400,000	13,500	1	55	3	45
				3	15	7	25
70	Rectal stricture, lymphogranuloma venereum	3,800,000	9,500	2	10	3	20
				3	55	6	40
71	Intestinal obstruction	4,150,000	12,500	1	40	3	35
				3	15	7	10

was started and after the patient had been given sulfathalidine for 5 days. The bleeding time (13) was determined by a puncture wound of the finger. The time of the appearance of the first drop of blood was noted. Each drop as it formed was removed with filter paper. The time that the bleeding stopped was noted. The time interval between the appearance of the first drop and the removal of the last represented the bleeding time.

Coagulation time (3) was determined in the following manner: Several drops of blood from a puncture wound of the finger were placed on 3 glass slides. At intervals of 15 seconds, a needle was drawn through one of the drops, when shreds of fibrin clung to the needle and were dragged along by it, coagulation had taken place and this time was then noted as coagulation time.

In 71 patients in the series bleeding and clotting time was observed before and after the administration of sulfathalidine therapy and the results are given in Table I. The first 5 patients received a dosage of 5 grams of sulfathalidine per day and the rest of the patients a dosage of ¼ gram of sulfathalidine per kilo in 6 divided doses.

In 29.5 per cent of the patients given sulfathalidine therapy there was an increase in the bleeding time of more than 2 minutes over the level before the drug was started, and in 53.5 per cent of the patients there was an increase of over 2 minutes in the clotting time. In 70.5

TABLE II.—INCREASE IN BLEEDING AND CLOTTING TIME IN 9 CASES

	Increase in bleeding time	Increase in clotting time
Over 1 minute	5	–
Over 2 minutes	3	4
Over 3 minutes	1	1
Over 4 minutes	–	2
Over 6 minutes	–	1
Over 8 minutes	–	1

TABLE III.—PATIENTS RECEIVING SULFATHALIDINE PLUS AN AMPULE OF VITAMIN K TWICE DAILY

Case No.	Diagnosis	Red blood count	White blood count	Bleeding time		Coagulation time	
				Min.	Sec.	Min.	Sec.
1	Inguinal hernia	4,200,000	7,500	2	15	4	15
				2	0	5	30
2	Rectal stricture, lymphogranuloma venereum	3,850,000	9,200	1	30	3	30
				2	15	4	10
3	Acute gangrenous appendicitis	4,300,000	15,200	1	45	4	0
				2	30	5	0
4	Rectal stricture, lymphogranuloma venereum	3,650,000	8,800	2	0	5	0
				2	15	5	15
5	Acute gangrenous appendicitis	4,100,000	16,400	2	0	4	15
				2	0	4	45
6	Rectal stricture, lymphogranuloma venereum	3,720,000	9,400	3	0	4	30
				2	45	4	30
7	Acute gangrenous appendicitis	3,950,000	17,500	1	30	3	30
				1	30	3	15
8	Carcinoma of stomach	2,950,000	7,400	1	45	3	0
				1	30	2	45
9	Rectal stricture, lymphogranuloma venereum	3,880,000	9,800	1	45	1	30
				4	30	4	30
10	Rectal stricture, lymphogranuloma venereum	3,450,000	7,800	3	30	5	0
				3	35	5	0
11	Carcinoma of sigmoid	3,250,000	6,400	2	30	5	0
				2	40	5	10
12	Carcinoma of rectum	3,530,000	8,700	3	0	6	35
				3	15	7	10
13	Carcinoma of rectum	3,300,000	7,200	1	50	6	0
				2	15	6	35
14	Acute gangrenous appendicitis	4,400,000	10,200	1	30	3	15
				3	20	5	30
15	Rectal stricture, lymphogranuloma venereum	3,980,000	7,900	1	45	2	45
				3	20	5	15
16	Stab wound of transverse colon	4,100,000	6,800	2	30	4	30
				2	45	4	45
17	Stab wound of ascending colon	4,200,000	7,500	3	10	5	30
				3	30	6	0
18	Intestinal obstruction	3,900,000	12,400	1	10	4	15
				3	30	7	0
19	Volvulus of sigmoid	3,900,000	9,600	2	15	3	45
				4	45	7	25
20	Intestinal obstruction	4,200,000	13,300	2	15	3	40
				2	30	4	15
21	Acute appendicitis	4,100,000	14,600	2	45	4	15
				3	0	4	45

TABLE III.—PATIENTS RECEIVING SULFATHALIDINE PLUS AN AMPULE OF VITAMIN K TWICE DAILY—Continued

Case No.	Diagnosis	Red blood count	White blood count	Bleeding time		Coagulation time	
				Min.	Sec.	Min.	Sec.
22	Multiple fistulae in ano	3,650,000	11,500	2	30	3	30
				2	45	3	30
23	Gunshot wound of abdomen and transverse colon	3,980,000	8,200	1	45	3	30
				3	45	6	0
24	Acute appendicitis	3,880,000	17,300	2	10	3	15
				2	45	3	30
25	Intestinal obstruction	3,750,000	11,400	1	45	3	30
				2	0	3	30
26	Fistula in ano	3,850,000	9,200	2	15	4	0
				4	15	7	0
27	Carcinoma of hepatic flexure	3,450,000	8,100	2	30	3	45
				2	15	3	45
28	Carcinoma of rectum	3,650,000	8,700	1	45	3	15
				3	0	6	15
29	Carcinoma of sigmoid	3,850,000	9,200	2	10	4	15
				2	0	4	0
30	Intestinal obstruction	4,200,000	10,500	2	45	4	15
				3	0	4	45

per cent of the patients there was an increase in the bleeding time of at least 1 minute over the time before sulfathalidine administration was started, and in 78.8 per cent of the patients receiving sulfathalidine ingestion there was an increase in the clotting time of over 1 minute.

Allen, as previously quoted, stated that in one-fifth of the patients with carcinoma of the colon he found that increased bleeding occurred after 4 to 5 days of sulfasuxidine administration. With sulfathalidine therapy we found an increase in the bleeding and clotting time in all 9 patients with carcinoma of the large bowel, as shown in Table II.

After we started to administer vitamin K to all patients receiving sulfathalidine therapy, we obtained the following results. In 7 patients with carcinoma there was no change in the bleeding and clotting time of 6. In 1 patient there was observed the following change: the bleeding time increased from 1 minute, 45 seconds, to 3 minutes, and the clotting time from 3 minutes, 15 seconds, to 6 minutes, 15 seconds.

We then started to give vitamin K, 5 milligrams twice per day, to the patients receiving sulfathalidine therapy, and in this group of 30 patients, there was no change in the bleeding or clotting time of 22 patients, or in only 8 cases was the bleeding and clotting time elevated, and then by only 1 minute. Thus, there was an increase in the bleeding time in 26.6 per cent of the patients who received vitamin K and sulfathalidine as compared to 70.5 per cent of the patients who did not receive vitamin K, and the clotting time was elevated in 26.6 per cent of the cases as compared to 78.8 per cent.

A detailed analysis of the results which were obtained in these cases is to be found in Table III.

CONCLUSIONS

From our observations of the bleeding and clotting time of 71 patients the following conclusions were reached:

1. When administered in therapeutic doses sulfathalidine increased the bleeding and clotting time in these cases.

2. The administration of vitamin K reduced this prolongation of the bleeding and clotting time in most instances.

3. All patients who receive sulfathalidine preoperatively and postoperatively should, at the same time, receive vitamin K in order to prevent a vitamin K deficiency and an increase in the bleeding and clotting time.

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ONE STAGE END-TO-END ANASTOMOSIS OF THE COLON

An Analysis of the Complications in 79 Cases with a Comparison of Open and Aseptic Types of Anastomoses

GEORGE P. ROSEMOND, M.D., F.A.C.S., W. EMORY BURNETT, M.D., F.A.C.S., and FRANCIS N. COOKE, M.D., Philadelphia, Pennsylvania

ONE hundred fifteen years ago, a French surgeon of Lyons, after experimental work on dogs, undertook the resection and one stage end-to-end anastomosis of the sigmoid colon in a patient afflicted with cancer. The patient survived the operation and lived until he succumbed to recurrence 1 year later. This occurred in the year 1833. Reports of this operation reached the ears of the members of the Royal Academy of Medicine in Paris, and in March of the year 1844, they dispatched a commission to Lyons in order to observe and report to the Academy the works of this Reybard of Lyons. In July of that year, the commission, Messrs. Blandin, Bevard, and Jobert de Lambelle (27), made their report. M. Reybard, lacking suitable clinical material, had demonstrated his technique on dogs. In all, 7 dogs were used in the demonstration. The results of this experiment were not good. Postmortem examinations revealed that adequate healing had not taken place between the ends of the anastomosed intestines. Some specimens had not healed at all, and in others, large fistulous openings were apparent. So, the commission concluded, since the procedure was so unsuccessful in experimental animals, was there any reason to believe that it would be more successful in man? The Academy thought not, and so the one stage end-to-end anastomosis of the colon as a method of treatment of carcinoma of the bowel was rejected by the Royal Academy of Medicine in Paris.

The history of colon surgery might have been entirely different had Reybard been acquainted with the work of one of his contemporaries, that of Antoine Lembert. M. Lembert reported to the surgical section of the Royal Academy of Medicine in Paris his experimental work on dogs in which he had devised a method of suture which allowed the intestinal wound edges to heal rapidly and with excellent approximation. Altogether he had operated upon 5 dogs. All 5 dogs lived. He further observed that the operative procedure in most of the dogs scarcely interrupted their normal habits of eating and elimination. This report was made January 26, 1826. This method of suture is the basis of our modern technique in intestinal surgery. We speak of it as the Lembert suture.

Since this early report on the works of M. Reybard to the French Royal Academy of Medicine, surgery of the colon has passed through many painful phases. Although colostomy was known and had been performed by Pillare (10) in 1776 and successfully by Duret (10), in 1793, surgical resection of the diseased colon had not been reported. In fact, during this period, the only relief offered patients suffering from cancer of the distal colon, according to Thomas Copeland, was the cauterization of the very painful hemorrhoids which developed "as a consequence of the obstructed circulation in the parts." Copeland described the late stage of the disease very accurately. He states "introduction of the finger into the rectum will be opposed by a hard ring of cartilagenous feel, composed of the diseased inner ring of the intestine." He also observed that despite vigorous treatment of the piles, the true nature of the disease went unrecognized. According to Dinnick, whose excellent and very thorough work, "The Origin and Evolution of Colostomy," was published in 1934, it was not until the middle of the 19th century that colostomy became widely used.

From the general surgery service, Temple University Hospital, and from the surgical service of Dr. W. Wayne Babcock, Temple University Hospital.

Abridgement of thesis submitted in March, 1948, by Dr. Cooke as required for the degree of M.S. in Surgery.

Dinnick states that Amussat (10), one of the foremost French surgeons of that time, "rescued (colostomy) from the realm of the occasional and heroic and advanced it to its proper place in surgery." In 1839, Amussat analyzed all the reported colostomies, of which there had been a total of 29 cases. From this critical survey and his own research into the anatomy of the colon, he published his concept of when and how colostomy should be performed. This teaching fell on fallow ground, and the palliative colostomy became the accepted method of treatment of carcinoma of the colon.

In the year 1882 Bryant described a procedure in which resection was done after exteriorization of a portion of the colon and 10 years later Bloch of Copenhagen utilized the same principle. In 1895 Paul of Liverpool reported to the British medical profession his historic series of 7 cases of exteriorization and resection of the colon. In the author's own words, this series represents the "education of a surgeon." Although the end-results in these cases were not good, the careful analysis given each case and the application to the next operation of that which had been learned from the preceding one led Paul to the development of the operative procedure which today bears his name. This procedure received even more widespread acclaim after the publication of the excellent work of Mikulicz in 1903. Because of this work and the way it was presented to the medical profession, this form of surgical treatment became known as the Mikulicz or the Mikulicz-Paul operation. The reason for this acclaim and almost universal acceptance of this procedure is obvious. At last some method of treating carcinoma of the colon had been devised which gave reasonable promise of curing the cancer without killing the patient. That dread scourge peritonitis, which attended all open intra-abdominal surgery, had been relegated to a minor role. Mortality had been reduced from an almost prohibitive level to a relatively benign 15 to 20 per cent by this method.

Surgery of the rectum and rectosigmoid had also made important strides. In the year 1885, just a few years after the first published papers on exteriorization and resection of the colon, Kraske (23) presented to the Fourteenth Congress of German Surgeons an operative procedure which bears his name, the Kraske perineal resection of carcinoma of the rectum. This method had many disadvantages, the most disturbing of which was the high percentage of recurrence of the tumor. Kraske himself realized this, and in 1906 he reported a series of 10 cases in which the original technique had been modified to include an abdominal procedure which mobilized the rectosigmoid and rectum prior to removal through the perineum. Miles went a step further and brought the colostomy out on the abdominal wall. There it was to remain until Babcock (2), in 1932, proposed that the colostomy be returned to the perineum whence it came. In addition to perineal colostomy, Babcock has long been a proponent of radical extirpation of carcinoma of the colon with preservation of functioning anal sphincters. Recent publications (3, 4) on this subject outline his technique in detail. A type of sphincter saving operation had been reported as early as 1923 by Lockhart-Mummery (16), who also called attention to the unnecessary sacrifice of the anal sphincters in many cases of carcinoma of the rectum and rectosigmoid.

At the turn of the century we see that medicine had advanced to the stage in which the objective was an attempt, by radical excision of the tumor and the adjacent tissues, to rid the patient of his cancer. Great strides had been made in surgery. This was a far cry from the hemorrhoidectomies of Copeland's time or the palliative colostomies of the 19th century. In spite of the excellent results reported by the advocates of these procedures, many surgeons still maintained an interest in an operation which would immediately re-establish continuity of the bowel following resection and thus eliminate the prolonged hospitalization and numerous surgical procedures necessitated by exteriorization of the bowel. As the anatomy and physiology of the intestinal tract became better understood, pioneering surgeons sought some method of colon anastomosis which would eliminate the troublesome Mikulicz and yet would not compromise the safety obtained by that procedure. Notable among these was the Johns Hopkins group, the members of which, led by Halsted, became very active in experi-

mental work on intestinal anastomosis. In 1910, Halsted published his paper on the bulkhead method of aseptic intestinal anastomosis. This was a very earnest effort to eliminate contamination at operation. In Halsted's own words, "for the large intestine the circular suture or end-to-end anastomosis would, if equally safe, be conceded to be the ideal method." Another method proposed by this group, utilizing the basting stitch principle, was published in the Johns Hopkins Hospital bulletin of 1908 by Parker and Kerr. The major obstacle to overcome in this suture and one which frequently occurred in experimental animals was the tendency for the formation of a diaphragm at the site of resection. All in all, these were important contributions and despite the disadvantages of each method, something was learned with each painstaking step.

In 1917, in a very excellent work, Lockhart-Mummery (17) described the technique which he utilized in open end-to-end anastomoses of the colon. By carefully packing off the peritoneal cavity at the time of operation and by careful attention to preoperative and postoperative care he believed that this procedure could be accomplished with reasonable success. The technique described in that treatise has scarcely been improved upon today.

In the years to follow, end-to-end anastomosis of the colon was not widely used. Instead the Mikulicz exteriorization principle for carcinoma of the colon was utilized by most clinics. For cancer of the rectosigmoid and rectum, in which exteriorization was impossible, the abdominoperineal resection of Miles became the accepted treatment.

In 1939 a very important contribution to colon surgery was made. Garlock and Seeley published their report on the effect of oral sulfanilamide on intestinal bacteria. Since that report, new and less toxic sulfanilamide products have been developed, and bacterial flora in the colon can be reduced to a minimum (26). At long last the proponents of one stage end-to-end anastomosis had added to their armamentarium the last necessary link. Peritonitis from contamination at operation had finally been successfully controlled.

Progress in colon surgery had been slow but steady. First began the development of the technique of intestinal surgery, the cornerstone of which was the development of the Lembert suture. Next, perhaps, was the gradual understanding by the medical profession of the anatomy and physiology of the gastrointestinal tract and, particularly, the absolute necessity for decompressive measures in cases of obstruction. This knowledge, coupled with the evolution of the blood bank and the development of modern anesthetic methods and finally the elimination of gross contamination at operation as a major factor, has brought us to the excellent method of treating carcinoma of the colon, first described by Reybard of Lyons 115 years ago.

TREATMENT IN 79 CASES

This paper is a survey of all end-to-end one stage anastomoses of the colon performed in the Temple University Hospital during the years 1945, 1946, and 1947. No ileocolectomies or perineal resections are included in this series.

There is no attempt in this paper to deal with the rate of cure in patients afflicted with carcinoma of the colon but rather to examine these cases from the standpoint of operative mortality, morbidity directly or indirectly contributed to by the operation, and finally, the end-results of the operative procedures. Altogether there have been 79 cases in which resection of the colon with one stage end-to-end anastomosis was done. The majority of the lesions for which resection was done were malignant. A few, 14 in number, were benign. Four of the patients, for reasons to be explained later, were reoperated upon and resection again carried out at the same site.

There were 6 deaths from all causes, which is a mortality rate of 7.5 per cent (Table I).

TABLE I.—DEATH IN 6 CASES

Cause of death	Case No.	Autopsy	Time, post operation
Coronary occlusion	81	yes	3 hours
	64	yes	12 days
Coronary occlusion and cerebral embolus from mural thrombus	42	yes	9 days
Peritonitis	73	no	18 days
Small bowel obstruction	50	yes	4 days
Sepsis (wound infection: pyelonephritis-B. pyocyaneus, septicemia-B. pyocyaneus	27	no	24 days

If the 2 cases of coronary occlusion and the 1 of cerebral embolus are excluded, the corrected mortality for 83 resections in 79 patients is 3.7 per cent.

Morbidity includes all complications, directly or indirectly resulting from the operative procedure in the entire postoperative period. These cases will be discussed in more detail later.

Preoperative preparation. The preparation of these patients for surgery followed the same general pattern; complete mechanical cleansing of the bowel by purgatives and enemas followed by oral sulfasuxidine or sulfathalidine, occasionally oral streptomycin, and a low residue diet. Blood chemistry and hemoglobin levels were corrected in this preoperative period when necessary. In a few of these patients obstruction was present when they were admitted to the hospital, and decompression was accomplished by either the Miller-Abbott tube and 100 per cent oxygen inhalations or some form of colostomy. The method of decompression utilized depended largely upon the degree of obstruction and its duration.

Technique. The surgical technique falls into two general classifications, the open method of anastomosis and the closed or aseptic method in which a Furness clamp or a modification of it was used.

In the open technique the operative field was protected from gross contamination by rubbershod Scudder clamps placed a comfortable distance from the severed ends of the bowel and complete isolation of the area with abdominal packs. In the majority of cases two rows of inverting sutures were used, although in a few cases, only one row of interrupted silk completed the anastomosis. Gloves were changed and clean instruments used after completion of this stage of the procedure. Twenty-eight anastomoses were performed in this manner. One of the patients had a proximal vent, in the form of a cecostomy, established at the time of operation. Four patients had a functioning colostomy previously established because of obstruction, when they came to the operating room.

The closed or aseptic technique made use of the Furness clamp and pin or a modification of it. One method (3, 14) of applying this clamp is to bring both segments of the bowel together at the site of proposed resection. The clamp is applied so that it includes both proximal and distal bowel with a loop above. The loop of bowel above the Furness clamp, which includes the diseased portion, is cut away below a Payr or another type of crushing clamp. When the Furness clamp is removed, the pin holds both proximal and distal segments of bowel. After the anastomosis the pin is removed and the lumen of the bowel re-established by the operator's fingers. The other method of aseptic anastomosis utilizes two Furness clamps and two pins. The bowel is resected between the two clamps. When the suturing is to begin the two pins are approximated and the sutures placed. In general two rows of sutures were used. Fifty-five closed anastomoses were performed in this series. In these 55 procedures there were 33 with proximal vents, either appendicostomy, cecostomy, or colostomy, established at the time of operation. Four patients came to operation with some form of functioning colostomy, which had been established previously because of obstruction.

Complications. Postoperative complications were many and varied. Those resulting in death have been listed. The case reports of the patients who died and of those contributing to the morbidity rate will be discussed in the following paragraphs.

CASE REPORTS

There were 3 cases of peritonitis. In 1 of these localization occurred and drainage was successful.

CASE 83. S. R., aged 53 years, male. The diagnosis was carcinoma of the descending colon, with no metastasis. Aseptic anastomosis without proximal vent was done. His progress was good, bowels began to move on the 3rd day after operation. On the 10th day a localized intra-abdominal abscess was drained through the outer edge of the wound. The patient was never very ill, but because of the localized peritonitis, was not discharged until the 24th postoperative day. The operative result was good.

The other 2 cases of peritonitis detailed in the following paragraphs are also listed in our mortality column.

CASE 73. D. R., aged 63 years, female. This patient had carcinoma of the descending colon. The

operation was resection and aseptic anastomosis with complemental appendicostomy. She was reoperated upon on the 8th postoperative day because of mechanical ileus, and at this time an ileostomy was done. Eleven days after the first operation the patient was operated upon again and drainage established for the peritonitis. She died of peritonitis on the 18th postoperative day. No autopsy was obtained. Although it was believed because of the findings at later operation that peritonitis was not a result of a leak at the colon anastomosis, this patient was signed out as death due to peritonitis following colon resection because of the lack of autopsy proof.

CASE 64. M. A., aged 67 years, female. The diagnosis in this case was colloid carcinoma of the transverse colon. Operation was resection and closed end-to-end aseptic anastomosis without proximal vent. Progress was apparently satisfactory until the third postoperative day when the temperature began to spike to 102. On the 6th postoperative day by x-ray examination the distention was interpreted as obstruction at the hepatic flexure. The patient was operated upon and cecostomy done. At operation turbid intraperitoneal fluid was found, positive culture, nonhemolytic Staphylococcus albus, also dilated small bowel. Cecum and terminal ileum were not distended. The patient responded slowly. Following cecostomy temperature continued to spike up to 102 daily. The patient was gotten out of bed and apparently was recovering with bowels moving well when she suddenly went into shock and died, 6 days after cecostomy and 12 days following resection. Autopsy revealed coronary thrombosis as the immediate cause of death. She also had minimal peritonitis from a small leak at the anastomosis.

In 6 cases, postoperative small bowel obstruction occurred.

In 2 of these cases there was evidence of obstruction in the immediate postoperative period which was successfully treated with the Miller-Abbott tube.

CASE 79. A. S., aged 48 years, female. Diagnosis was carcinoma of the rectosigmoid. Operation was resection and open end-to-end anastomosis without proximal vent. The patient responded well until the 4th postoperative day when distention became evident, and the next day x-ray examination revealed small bowel obstruction. Miller-Abbott tube was passed and obstruction was relieved. The patient was discharged on the 15th postoperative day.

CASE 67. D. S., aged 48 years, male. This case will be discussed in more detail under late obstructions. It is included here because the Miller-Abbott tube was used until the 22nd postoperative day. Following the removal of the tube the patient was discharged in apparently good condition.

In 1 case a cecostomy was done 3 days after operation.

CASE 1. M. S., aged 63 years, male. The diagnosis was carcinoma of the sigmoid. The lesion was resected and a closed type anastomosis without a proximal vent was performed. The patient showed evidence of distention early in the postoperative period. This was unrelieved by the Miller-Abbott tube and on the 3rd day a cecostomy was done as a decompressive measure. Following this, the patient's condition improved and, except for a febrile response, the postoperative course was smooth.

The following cases were readmissions of patients who had developed ileus a considerable time after resection. This type of complication can and does follow any type of abdominal surgery but for the sake of completeness they are included here.

CASE 8. C. H., aged 56 years, female. Diverticulitis of the sigmoid was diagnosed. Resection and aseptic end-to-end anastomosis with complemental cecostomy were performed. The patient apparently had an uneventful postoperative course, was on liquids on the second day, and soft diet on the sixth day. She was discharged on the 28th postoperative day. No reason is given on the chart for this prolonged stay. Presumably the patient wished to remain until the cecostomy was completely healed. Nine months later she was readmitted with chronic obstruction. Operation revealed many dense adhesions about the old scars (hysterectomy and sigmoidectomy). Separation of these adhesions apparently relieved the patient's symptoms. She has been well for 18 months.

CASE 67. D. S., aged 48 years, male. Volvulus recurrent, with stenosis at the base of the volvulus was the diagnosis in this case. After adequate preparation, the redundant sigmoid was resected and an open end-to-end anastomosis done without proximal vent. A Miller-Abbott tube had been passed preoperatively. The course in the hospital was not uneventful. Each attempt to close the Miller-Abbott resulted in abdominal distention. Although the patient was taking food well, the Miller-Abbott tube was not removed until the 22nd day. The impression was that the small bowel had been obstructed by adhesions. After being free of symptoms, this patient was readmitted 18 months later with obvious mechanical small bowel obstruction. Operation revealed a narrow adhesion obstructing the lower jejunum. Smooth postoperative course followed lysis of this adhesive band. There has been no recurrence of symptoms.

The other 2 cases of intestinal obstruction are listed in our mortality column.

CASE 50. J. H., aged 73 years, male. This patient had carcinoma of the transverse colon. After suitable preparation, resection of the tumor and an aseptic end-to-end anastomosis was done without a proximal vent. The patient responded well after operation and was making an apparently normal re-

covery until the 3rd postoperative night when he complained of abdominal pain and began to vomit. This condition went unrecognized until the following morning at which time the patient was quite ill and in a state of vascular collapse. Under local anesthesia, the abdomen was explored and a high intestinal obstruction was found. The walls of the distended jejunum were dusky blue in color. The obstruction was relieved but the patient failed to respond and died a few hours later. Autopsy was obtained and corroborated the clinical findings.

CASE 73. D. R., aged 63 years, female. This case has already been described under peritonitis which was the cause of death, although a small bowel obstruction was found at second operation. Autopsy was not obtained and complete analysis is, therefore, impossible.

Failure of the anastomosis to function occurred in 4 cases. These are described in detail below.

CASE 63. A. S., aged 43 years, male. Diagnosis was ulcerative colitis. The distal two-thirds of the transverse colon, descending colon, and the proximal two-thirds of the sigmoid were resected. Anastomosis between proximal transverse colon and distal sigmoid was the open type. A functioning ileostomy had previously been established. The postoperative course was completely uneventful. Sixteen months later the patient was readmitted because of obstruction. Operation at this time revealed that extreme tension between the transverse colon and sigmoid had elongated and narrowed the lumen to such an extent that it was partially obstructed. A resection and closed end-to-end anastomosis was done with complemental appendicostomy. Postoperative course was uneventful and patient was discharged on the 20th day.

CASE 10. M. P., aged 38 years, female. Carcinoma of the sigmoid was the diagnosis. The sigmoid was resected and an aseptic end-to-end anastomosis performed with complemental cecostomy. The postoperative course was good for the first few days. The cecostomy was allowed to close. On the 17th day, it was apparent that there was obstruction at the site of the anastomosis and a colostomy was done. Four weeks after the original operation another resection was carried out and an aseptic closure made. The excised specimen showed a complete diaphragm had formed at the site of the original anastomosis. The course following this procedure was uneventful and the patient was discharged on the 12th day.

CASE 29. M. P., aged 62 years, female. Diagnosis was redundant sigmoid—obstipation, severe. After adequate preparation the sigmoid was resected and an aseptic end-to-end anastomosis performed with complemental cecostomy. The patient responded well for the first few days, but it soon became apparent that something was wrong at the site of anastomosis. Obstipation persisted despite efforts to stimulate movement via the cecostomy. The temperature and pulse were normal, however, and the patient was not ill. On the seventh day she was reoperated upon. A small area of necrosis was found at the site of resection. A rectal tube was passed from below up through the anastomosis and a drain placed retroperitoneally down to the suture line. Following this maneuver, the patient made a normal recovery.

CASE 56. H. K., aged 60 years, male. This patient had had several operations for peptic ulcer elsewhere. On admission there was evidence of gastrocolic fistula. At operation, an anterior and a posterior gastroenterostomy were found. The loop encircled and compressed the colon. A marginal ulcer with colonic fistula and a chronically perforating duodenal ulcer were present. A partial gastrectomy with resection of the involved jejunum was completed. The obstructed colon was then resected and an aseptic end-to-end anastomosis was performed without a proximal vent. The patient responded well but on the 7th day it was evident, clinically and by x-ray examination, that obstruction existed at the site of colon anastomosis. A cecostomy was done. On the 27th day a plastic procedure on the colon established an adequate lumen. The patient was discharged with a good operative result.

There were 3 cases of coronary occlusion. Two of these are of particular interest because they occurred just a few hours after completion of operation.

CASE 81. F. W., aged 70 years, male. Diagnosis was carcinoma of the sigmoid. In addition the patient had hypertension (admission blood pressure 186/98) and gave a history of having had a coronary occlusion 3 years before admission. After suitable preoperative preparation the patient was operated upon and an aseptic end-to-end anastomosis with a complemental cecostomy was performed. During the operation, which was done under spinal anesthesia, the blood pressure dropped to 75/50 where it remained for 30 minutes. It gradually rose until at the end of an hour and 15 minutes it had risen to 115/70. The patient was returned to his room in apparently good condition. Two hours later he suffered a heart attack and died 3 hours after operation. Autopsy revealed the suspected coronary occlusion.

CASE 42. F. H., aged 57 years, male. Diagnosis was carcinoma of the sigmoid partially obstructing. The obstruction was relieved by the Miller-Abbott tube, enemas, and oxygen inhalations. After suitable preparation the patient was operated upon and resection of the sigmoid in the open manner without a proximal vent was performed. During the operative procedure the blood pressure remained fairly constant. Before anesthesia, continuous spinal, the blood pressure was 90/70. Twenty minutes after the spinal was given, the pressure dropped to 70/50 where it remained for 20 minutes. Toward the end of the procedure it again dropped to 70/50 where it

remained for 15 minutes. With stimulants it rose to 100/70. One hour and 30 minutes after operation the patient experienced severe substernal pain. Electrocardiogram revealed a posterior infarction. The cardiac disease responded to therapy and the anastomosis was functioning well, soft diet, and bowels moving, until the evening of the 8th day at which time the patient had a cerebral accident. Twenty-four hours later there was extension of this process and the patient died. Autopsy revealed a cerebral embolus, originating probably from the mural thrombus, as the cause of death. The myocardial infarction was demonstrated.

These cases of coronary occlusion which occurred within a few hours after operation cannot be dismissed with a wave of the hand and classified as unavoidable catastrophes. In both of these patients a cardiac history was obtained. In the first case a definite history of infarction was given and in the second a history of anginal pain of such magnitude that the patient had seen a cardiologist was discovered after operation. Both patients were cardiac problems before they developed cancer. The type of anesthesia to be used in such cases is always a problem. Spinal was used in both cases. The wisdom of this choice is open to question. The important point is to see that there is no drop in blood pressure for an appreciable period during the operative procedure. In any event in a certain percentage of these cases death will result from cardiac disease.

The third case of coronary occlusion has already been reported under peritonitis. That is Case 64. The occlusion was brought on in all probability by the patient's stormy postoperative course.

Several other cases presented complications which should be considered.

The following case is listed in our mortality column.

CASE 27. E. R., aged 68 years, female. The diagnosis was carcinoma of the sigmoid with complete obstruction on admission. From the history, the duration of the obstruction was 3 weeks. Cecostomy was performed as a decompressive measure. The patient was quite ill and 2 weeks were spent in preparation for definitive surgery. The sigmoid was resected and open anastomosis done. Preparation of the bowel was definitely not good. The cecostomy was inadequate. The immediate postoperative period was fairly good, despite the fact that there was a temperature elevation up to 104. On the 9th day a urine culture was positive and the urine was loaded with pus cells. During this period the patient was having on the average of three stools per day. Careful examination of the operative site revealed no evidence of intra-abdominal infection. The wound was superficially infected. Temperature began to rise on the 10th day. The organisms (Bacillus pyocyaneus) in the urine and wound failed to respond to antibiotics. This situation continued and the patient died on the 24th day. Prior to death a positive blood culture of Bacillus pyocyaneus was obtained. This death was attributed to sepsis. No autopsy was obtained.

Urinary fistula occurred in 1 case.

CASE 37. F. M., aged 51 years, female. Diagnosis was sigmoid carcinoma. The patient was adequately prepared and resection with an aseptic anastomosis with complemental cecostomy was performed. During the operative procedure the left ureter was divided and anastomosed. In the postoperative period the patient developed urinary fistula and later it became necessary to do a nephrectomy. She recovered and has remained well since.

In the next case the patient developed a fecal fistula.

CASE 12. J. R., aged 59 years, female. This patient had diverticulitis of the sigmoid. She was admitted with two colostomies, one at the sigmoid and the other at the ascending colon. In addition this patient had fistulous tracts and abdominal wall abscesses. After incision and drainage of the abscesses and adequate preparation of the bowel a closed type of resection was done at which time the sigmoid colostomy was eliminated. The postoperative course was not eventful and after closure of the colostomy the patient was discharged. Two months later she was readmitted. A fecal fistula had developed at the site of the sigmoid anastomosis. After adequate drainage of this tract and preparation of the bowel the involved area was resected and an open anastomosis done with complemental appendicostomy. Recovery was uneventful.

The following case is presented because two resections were done at the same site.

CASE 70. J. S., aged 59 years, male. Diagnosis was carcinoma of the sigmoid. After adequate preparation the sigmoid was resected and anastomosed openly without a proximal vent. Postoperative course was uneventful. Microscopic examination revealed that tumor existed in the cut edge of some of the tissue removed and so on the 12th day the patient was reoperated upon and resection again done at the same site. Open anastomosis without proximal vent was performed. Recovery was otherwise uneventful. A superficial abscess was drained on the 7th day. Patient was discharged on the 14th day.

There were no cases of pulmonary embolism in this group, but 2 patients developed signs and symptoms of phlebothrombosis. Neither of these cases was serious and both responded well to anticoagulant therapy.

CASE 52. A. C., aged 71 years, female. Diagnosis was carcinoma of the transverse colon which, on admission, was causing obstruction. The obstruction was relieved by use of the Miller-Abbott tube and enemas. The patient was operated upon and aseptic anastomosis accomplished without proximal vent. At the time of operation the Miller-Abbott tube was at the site of the lesion. Postoperative course was uneventful except for signs and symptoms of phlebothrombosis which became apparent on the 7th day. This was successfully treated with anticoagulants and the patient was discharged on the 11th day.

CASE 43. B. W., aged 64 years, male. The diagnosis was carcinoma of the rectosigmoid. Resection and open end-to-end anastomosis of the upper sigmoid to the rectum without proximal vent were performed. Rectal tube was passed through the anastomosis from below at operation. The postoperative course was marred by atelectasis and on the 12th day diarrhea became a troublesome complaint. The patient had an indwelling catheter postoperatively because of retention, and attempts to remove this were fruitless and he was discharged with catheter in place. Also while in the hospital he showed some tenderness in the left calf which was interpreted as phlebothrombosis. This responded to heparin and dicumarol. Three months later these complaints had disappeared.

In the following case the patient developed a wound infection of such magnitude that his hospital stay was prolonged until the 29th postoperative day.

CASE 16. S. C., aged 75 years, male. After suitable preparation a closed resection and anastomosis with complemental appendicostomy were done. The patient responded well except for a temperature elevation to 102.6 on the second day. On the 4th day it was 103; despite this the patient was on surgical liquids and his bowels had moved twice. He continued to improve and his temperature elevation declined by lysis. On the 20th day a large abscess was found in the lower edge of the incision and drained. He was discharged on the 29th day.

The inclusion of this complication under wound infection rather than under localized peritonitis is open to question. The fact that ileus was not present in an unusual degree has persuaded us to classify this case as one of wound infection.

CARCINOMA OF THE RECTOSIGMOID

Resection of lesions in the rectosigmoid should rightly be considered as a separate group. This method of anterior resection and end-to-end anastomosis was used in 8 cases. Six of these 8 procedures were performed in the last year of this 3 year report. The technique as advocated in recent years by Dixon was modified somewhat. In none of these cases was the pelvic peritoneum approximated over or about the anastomosis and in none was a presacral drain utilized. The technique used varied only in the type of anastomosis and whether or not use was made of a proximal vent as a complemental procedure.

In 5 cases resection and anastomosis were carried out in the aseptic manner with complemental appendicostomy or cecostomy. In the 3 remaining cases resection and anastomosis were by the open technique without a proximal vent. In all 3 of these cases a rectal tube was passed from below up through the anastomosis at the time of operation. This maneuver, which has been described by Waugh and Custer and prior to them by Stone and McLanahan, has also been very useful in our hands.

Complications in this group of 8 cases have been remarkably few. No evidence of peritonitis developed and fecal fistulas were notably absent. One patient, Case 43, with carcinoma of the rectosigmoid who had an open type anastomosis without proximal vent with rectal tube through anastomosis, already described under phlebothrombosis, developed a troublesome diarrhea on the 12th postoperative day. In addition he had urinary retention and at one time in his early postoperative period he developed atelectasis. With treatment these complaints disappeared.

The only other complication was in Case 79, with carcinoma of the rectosigmoid. Operation was open anastomosis without proximal vent with a rectal tube through the anastomosis. This patient developed postoperative ileus which responded promptly to intubation. This case is described under intestinal obstruction.

These postoperative complications were not of a serious or lasting nature and the operative results have been good.

SUMMARY AND CONCLUSIONS

In summarizing this report our attention is first directed to the 6 patients who died as a result of the operative procedure. There were 3 cases of coronary occlusion. Two of the 3 cases of occlusion occurred within a few hours after operation. Both of these patients came to operation with definite cardiac disease. Myocardial disease is not an uncommon finding in patients in this age group, and every effort should be made to evaluate their cardiac status before operation. In every situation in which cardiac disease is present, it is imperative that all precautions be taken to prevent embarrassment of the coronary circulation. A drop in blood pressure from whatever cause, anesthesia or prolonged surgery, should require the urgent attention of all concerned. Only in this way will this type of mortality be reduced. In all probability, the third case of coronary occlusion occurred as a result of the undue strain put upon the heart by the stormy postoperative course. This must, of course, be considered a preventable death.

In the case of the 1 patient who died of small bowel obstruction, we were guilty of an error in management. This patient died because the obstruction existed, unrecognized, for 12 hours.

One patient died of sepsis. This patient had remained at home with an obstruction for 3 weeks before admission. It is not easy to classify this as a preventable death. If there was an error, it was probably due to the fact that a permanent type of colostomy was not done for decompression, and perhaps a much longer time should have been allowed to lapse before definitive surgery was attempted.

The 1 case of peritonitis must, of course, be considered a technical failure.

Review of the statistics brings to light some very interesting facts. In comparing the two general types of anastomosis, it is noteworthy that peritonitis was not evident in any of the 28 cases of open end-to-end anastomoses. Three cases of peritonitis occurred in the group of aseptic or closed anastomoses. Of the 4 cases in which the anastomosis failed to function, 3 were in the closed and 1 in the open group. Open anastomosis as a routine procedure has been reported by some authors (1, 18, 19, 20, 31). In our small series, conclusions are dangerous but speculations are certainly in order. Since these cases represent the surgical techniques of a group rather than an individual, the speculations become even more justifiable. One explanation of our results is that, all things being equal, it will probably be conceded by most surgeons that a more exact suture can be placed in an open type of anastomosis than in a closed type.

The question of establishing a proximal vent or safety valve at the time of operation has always been a controversial one. As so often is the case in surgery, time modifies some of our most pronounced convictions. In 1931, in reviewing all of the colon cases in Peter Bent Brigham Hospital, Cheever wrote "... no surgeon of experience would advise as a routine, primary resection with suture-anastomosis in the distal colon without making a proximal safety valve." In the same article the author expressed doubt of the efficacy of a proximal vent in the right sided colon resections. Fourteen years later Wangensteen states, "... (complemental) colostomy is not necessary"; and Waugh and Custer, "There is little question in our minds that colostomy is an unnecessary addition to resection performed for lesions of the sigmoid or above. However, our feeling in regard to its use in lower lying lesions is not so definite." In that same year, in their report on 173 cases of carcinoma of the colon, Coller and Vaughn concluded that a complementary cecostomy is a wise safeguard in primary resection of the colon.

In our series complemental vents were established in 52 of the 83 resections. If we eliminate the postoperative complications which were remote from the operative site, such as coronary occlusion and phlebothrombosis, and carefully analyze the remaining 13 complicated cases, we find the following facts. There were 6 cases in which a proximal vent as a complemental procedure was not established. In only 3 of these would a proximal vent have conceivably been of any benefit. In 2 of these 3 cases cecostomy was done with good results. In the third case the localized infection was at no time severe enough to warrant intervention. In the 7 cases in which

a proximal vent was established as a complemental procedure, there were 3 in which the proximal vent was of obvious benefit.

In the light of these figures the following conclusions seem justifiable.

In low lesions a tube through the anastomosis seems to eliminate the necessity of a proximal vent.

In uncomplicated resections in which adequate lumen and undoubted blood supply to the parts are assured a proximal vent is an unnecessary maneuver.

In cases in which trouble develops at the suture line, such as obstruction or leakage, a proximal vent is a valuable adjunct, but it seems reasonable to assume that such a vent could be established as the necessity arose rather than as a routine procedure.

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PSEUDOCYSTS OF THE PANCREAS

Report of 31 Cases

KARL A. MEYER, M.D., F.A.C.S., Chicago, Illinois, ALFRED I. SHERIDAN, M.D., Seattle, Washington, and RICHARD F. MURPHY, M.D., Chicago, Illinois

EVER since 1761 when Morgagni first described the multiple cysts of the pancreas, mesentery, and omentum which he found in a cadaver, the etiology, diagnosis, and treatment of pancreatic cysts has continued to be a challenging problem. Even such a basic prerequisite to the solution of this fascinating problem as an adequate pathological classification of pancreatic cysts has been impeded by difficulties which have not yet been overcome. The confusion in pathological terminology has resulted from disagreement regarding the origin and pathogenesis of the cysts.

Of all the pancreatic cysts, the so called "pseudocysts" have been the most difficult to define properly. The term pseudocyst has usually been given to encysted fluid collections in the peripancreatic tissues of the lesser omental sac. The absence of an epithelial lining of the fibrous connective tissue wall of the pseudocyst has been used to differentiate it from true pancreatic cysts such as cystadenomas, retention and proliferation cysts. But this differential criterion is not infallible and may lead to an erroneous pathological diagnosis. For example, a large retention cyst may be indistinguishable from a pseudocyst if its epithelial lining should undergo pressure atrophy. Further, it is possible that some pancreatic pseudocysts possess an epithelial lining which subsequently is destroyed by activated pancreatic enzymes or atrophies from pressure. Such possibilities as these make an accurate pathological diagnosis, based upon the presence of an epithelial lining, impossible in all pancreatic cysts.

Another intriguing aspect of pancreatic cysts is the observation that the pancreas is the only parenchymatous organ in the body which reacts to trauma or inflammation by self destruction and the formation of a pseudocyst. Several reasons for this immediately suggest themselves. First, its anatomical position astride the vertebral column makes it particularly vulnerable to blunt trauma. Second, the pancreas responds to trauma or inflammation by pouring out large amounts of fluid which may or may not contain activated enzymes. The abundant blood supply of the pancreas and its ability to secrete approximately 800 cubic centimeters of pancreatic juice per day in the average adult seem to account for its profuse secretion when injured or inflamed. The presence of this irritating pancreatic secretion in the lesser omental sac appears to provoke a chemical peritonitis with a further outpouring of inflammatory fluid which eventually becomes encysted.

The most compelling phase of the problem of pancreatic pseudocysts is the surgical treatment. At present, sharp differences of opinion exist regarding the employment of complete excision, marsupialization or internal drainage of these cysts. The multiplicity of opinions as to the most desirable surgical procedure prompted us to review our experience with pseudocysts in an effort to evaluate the results of the procedures employed. From 1930 to 1947 inclusive, 31 pseudocysts were operated upon at the Cook County Hospital and on the private service of one of us (KAM). Pseudocysts which have been previously reported in the literature are found in Table I.

ETIOLOGICAL FACTORS

A division of our 31 cases, according to sex, showed an equal distribution between male and female: 15 cases (48.4%) occurred in male patients while 16 cases (51.6%) occurred in female patients. This distribution differs from the experience of Rabinovitch and Pines

From the Department of Surgery, Northwestern University Medical School, Cook County Hospital and the Cook County Graduate School of Medicine.

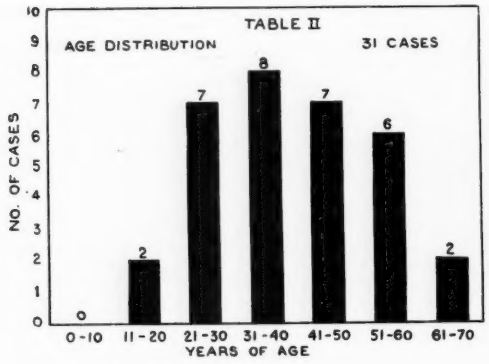

Chart 1. Age distribution in 31 cases.

who found all of their 11 cases in female patients. This preponderance of female patients in their series may be explained by the fact that none of their patients suffered trauma, and the incidence of associated chronic cholecystitis and acute and chronic pancreatitis was high. These latter conditions are statistically more common in females.

The age distribution of the 31 cases is recorded in Chart 1. An analysis of the ages of the patients revealed a fairly even distribution between the ages of 20 and 60. The youngest patient was 14 years old and the oldest was 64 year old and the average age was 40.6 years. Telling and Dobson reported a pancreatic cyst in an 11 month old child. A congenital cyst of the pancreas without an epithelial lining was reported in a 5 month old infant by Eha.

A summary of the racial distribution revealed that 23 cases (74%) occurred in white patients while 8 cases (26%) occurred in negro patients. A survey of hospital admissions during these years showed that approximately the same proportion of white and colored patient admissions existed. Therefore no marked racial predilection was observed.

Blunt trauma to the pancreas, acute and chronic cholecystitis and acute and chronic pancreatitis are frequently associated with pseudocysts. Both clinical and experimental evidence is available which suggests that these factors are responsible for the production of pseudocysts. Lazarus experimentally produced a pseudocyst in a dog by crushing the pancreas. A hematoma formed which later became an encapsulated cyst containing 100 cubic centimeters of milky fluid.

TABLE 1.—PSEUDOCYSTS PREVIOUSLY REPORTED

Author	Year	No. of cases
Lloyd	1892	2
Koerte	1911	117**
Kerr	1919	2
Judd	1921	41
Eha	1922	1
Einhorn	1925	2
McWhorter	1925	6††
Friedenthal and Cullen	1926	2
Judd, Matson, Mahorner	1931	47
Gordin	1937	1
Meyer	1939	13
Koucky, et al.	1941	4
Rabinovitch and Pines	1942	11
Chesterman	1943	1
Pinkham	1945	10
Adams and Nishijima	1946	6
Carter and Slattery	1947	3

**Collected from the literature.
††Collected from members of Chicago Surgical Society.

In our series, a history of trauma was elicited in 16 (51.6%) of the 31 cases. Koerte obtained a history of trauma in 33 (28%) out of 117 cases. Judd (17) noted trauma in only 1 of his 44 cases. More recently, Pinkham stated that trauma occurs in 20 per cent, or less, of cases. A possible explanation of the higher incidence of trauma in our series is the fact that our patients are drawn from an indigent population which is more prone to incur trauma. The time interval between the traumatic incident and the discovery of the pseudocyst averaged 5 months. The shortest time was 24 hours and the longest was 4 years. The trauma to the abdomen was severe in all cases and resulted from a variety of injuries, such as: kick in the abdomen, 4; automobile accident, 4; punch in abdomen, 5; fall on iron post, struck by baseball and not recorded each 1 case.

Cholecystitis and pancreatitis appeared to be etiological factors in 6 of our cases (16.1%). Cholelithiasis and chronic cholecystitis was found at surgery in 3 cases. In 1 case, acute cholecystitis was observed at surgery. A history suggestive of acute pancreatitis was obtained in 2 cases. The incidence of biliary and pancreatic disease was somewhat lower in our series than is reported by other authors. Adams and Nishijima reported cholelithiasis in 2 (40%) of their 5 cases. Pinkham reported

Fig. 1. Barium meal shows alteration of rugal pattern in pyloric region.

Fig. 2. Anteroposterior roentgenogram shows the upward displacement of the pyloric region.

6 cases (60%) out of 10, in which the pseudocyst was associated with pancreatitis and in 4 of these (40%) there was concurrent biliary tract disease. Judd (17) reported 17 (36%) out of 47 pancreatic cysts had biliary tract disease. Archibald (2) also noted the frequent association of biliary tract disease with bile pancreatitis and subsequent necrosis and pseudocyst formation. McWhorter reported 2 cases (33%) out of 6 in which the pseudocyst followed pancreatitis. From these data it is apparent that the etiological relationship of trauma, cholecystitis and pancreatitis to pseudocyst formation in our series coincides with the prevailing clinical impression on this point.

PATHOLOGY

The pathogenesis of pseudocysts, as the discussion of their etiology has indicated, is intimately related to trauma to the pancreas and to cholecystitis and pancreatitis. A consideration of the etiology of acute pancreatitis and its relation to cholecystitis is not within the scope of this paper. For further information regarding this subject, the reader is referred to the excellent papers of Opie, Archibald (2), Dragstedt, and Rich and Duff. Whatever the inciting agent may be, the response of the pancreas to acinar damage is an escape and activation of trypsinogen and lipase with progressive, focal necrosis and hemorrhage in the parenchyma of the gland. When this process of necrosis reaches the anterior surface of the gland, it ruptures into the lesser omental sac where it produces a chemical peritonitis with a profuse inflammatory exudate from the adjacent serosal and peritoneal surfaces. If the foramen of Winslow is sealed off by this exudate, the lesser omental sac is converted into a closed space within whose confines the exudate becomes encapsulated by the proliferation of fibrous connective tissue from the adjacent mesothelium-lined surfaces during the reparative

Fig. 3. Oblique roentgenogram shows marked deformity of the posterior wall of the stomach by a retrogastric radiopaque mass.

phase of the inflammatory process. The fibrous connective tissue which forms the cyst wall has numerous strands and dense adhesions to its parent surfaces, namely the structures which delimit the lesser omental sac. It is these adhesions which make complete excision of a large pseudocyst a difficult procedure. Carter and Slattery reported 2 cases in which the common duct was inadvertently opened during the excision of a pseudocyst. From the foregoing it is evident that the pathogenesis of pseudocysts is incumbent upon the response of the pancreas to injury by enzymatic autolysis and upon the location of the gland in a potentially closed space.

The position of the pseudocysts has been well described in previous papers. In our series the cyst presented itself through the gastrocolic omentum most frequently and through the gastrohepatic omentum less often. A retrogastric position of the cyst with the stomach pushed forward occurred with a frequency equal to the gastrohepatic presentation. In one case the cyst presented itself through the gastrosplenic ligament, displacing the stomach anteriorly and to the right. In one instance the cyst presented in a retrogastric position causing the stomach to be tautly flattened over the cyst wall and producing pyloric obstruction. The excessive, frequent vomiting which occurred in this patient plus a previous laparotomy scar on the upper abdomen led to the erroneous diagnosis of high intestinal obstruction.

The relation of the cyst to the various sectors of the anterior abdominal wall was as follows: In 2 cases, the presence or absence of a mass was not recorded. In 3 of the remaining 29 cases (10.5%), no mass was palpated. In 12 (46%) of the 26 cases in which a mass was noted, it was found in the left hypochondrium. The mass occupied the epigastrium next most frequently, being present there in 8 cases (31%). In no instance was the mass observed below the umbilicus. The mass appeared in the right hypochondrium in 1 case; in the epigastrium and right hypochondrium in 2 cases, in the epigastrium and left hypochondrium in 3 cases.

The amount of fluid contained in the cyst varied in the 16 cases in which it was measured. The smallest amount was 15 cubic centimeters and the largest 7,000 cubic centimeters. The average was 2,686 cubic centimeters. The color of the fluid was chocolate brown in 39 per cent, yellow or straw colored in 39 per cent, milky in 11 per cent, and hemorrhagic in 11 per cent. Pancreatic enzymes in the cyst fluid were tested for in 12 cases. In 9 of these (75%), enzymes were present and amylase, trypsin, and lipase were found. Rabinovitch and Pines reported the presence of enzymes in 9 of their 11 cases. In the remaining 2 cases, the tests were not performed.

X-RAY AND LABORATORY AIDS IN DIAGNOSIS

In the diagnosis of pseudocysts, x-ray films proved far more useful in our hands than did laboratory tests. In the 8 cases in which scout films of the abdomen were taken, a radiopaque mass was evident in 7. A barium meal was given in 14 cases and in 13 of these the

Fig. 4. Abdomen opened exposing the stomach displaced anteriorly by the retrogastric cyst.

Fig. 5. Cyst exposed by division of the gastrocolic omentum and dissected from the posterior surface of the stomach. Note the roughened area on the stomach with numerous vessels ligated where the cyst was adherent.

stomach was displaced (Figs. 1 to 3). In this regard, it is interesting to note that Pinkham reported the use of gastric pneumograms to outline the pseudocyst. A barium enema was administered in 7 cases and the transverse colon was displaced in 6 of these.

Glycosuria was not detected in the routine urinalyses made in the 31 patients. The blood sugar level was determined in 6 cases and was found to be within normal limits.

A serum amylase determination was made in 8 cases. In 2 of these cases (25%), the amylase was elevated preoperatively to 124 and 96 units, respectively. In both cases a ruptured cyst was found at operation. In 1 of these ruptured cysts, one in which the pseudocyst followed an acute pancreatitis, the serum amylase was elevated to 148 units on the fifteenth day after marsupialization. Pinkham noted an elevated preoperative serum amylase in 6 of his cases which dropped promptly after drainage in 4 cases. It is Pinkham's opinion that a sustained elevation of the serum amylase after acute pancreatitis is suggestive of the development of a pseudocyst.

SURGICAL TREATMENT

The first recorded attempt to treat a pancreatic cyst surgically was made by Le Dentu in 1862 (17). He punctured and drained the cyst but peritonitis developed subsequently and the patient died. Similarly, Lucke (17) in 1866 drained a pancreatic cyst and the patient died. Not until 1861, when Bozeman (17) extirpated a pancreatic cyst, was the first successful operation performed. Gussenbauer (17), a pupil of Billroth's, in 1882 performed the first marsupialization of a cyst with success. Marsupialization was the only surgical procedure performed for pseudocysts until 1927 when Hahn anastomosed the cyst to the jejunum. In 1927, Walzel, anastomosed the cyst to the gall bladder and ligated the cystic duct to prevent bile from entering the cyst. In 1931 Jurasz and Jedlicka each reported a case in which the pseudocyst had been anastomosed to the stomach. Judd, Matson, and Mahorner (17) reported 47 cases in 1931. Seven of these cysts were completely excised, 33 were marsupialized, 6 were partly excised and drained, and 1 cyst was malignant and

Fig. 6. Further dissection of the cyst abandoned at this point because of dense adhesions to the middle colic artery.

Fig. 7. Cyst has been opened and aspirated revealing a smooth lining without papillary growths.

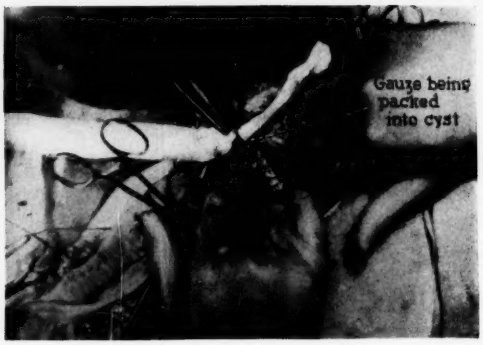

Fig. 8. Cyst wall held with forceps while gauze pack was inserted.

inoperable. In 1935, Kirschner reported an anastomosis of a cyst to the duodenum. Neuffer in 1939, anastomosed a cyst to the gall bladder without ligating the cystic duct. One of us (KAM) (24) reported 13 cases in 1939, and in 3 of these the cyst was successfully anastomosed to the gall bladder, the technique described by Neuffer being used. Pinkham in 1939 reported 10 pseudocysts, all of which were marsupialized successfully.

More recently, Chesterman, in 1943, rereported a successful anastomosis of a pseudocyst to the jejunum. In 1946, Adams and Nishijima reported 6 pseudocysts. Two of these were completely excised, 1 was anastomosed to the jejunum, 2 were drained externally and one was first drained externally and the fistula subsequently implanted into the jejunum. Carter and Slattery, in 1947, reported 2 cases in which a pseudocyst was completely excised and a third case in which the cyst was anastomosed over a T-tube to an accidental rent in the common duct.

In our series of 31 cases a total of 33 operative procedures were performed, one patient undergoing 3 procedures. The types of procedures which were employed are as follows: marsupialization, 25 cases; cystocholecystostomy, 4 cases; cystojejunostomy, 2 cases; complete excision, 2 cases.

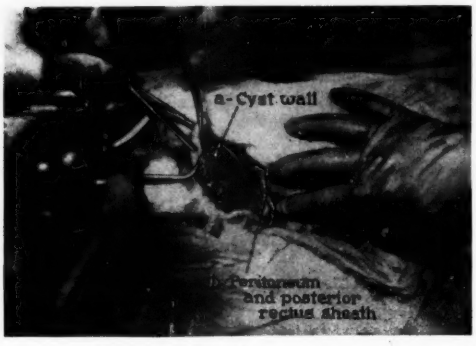

Fig. 9. Cyst marsupialized by suturing cyst wall, *a*, to the peritoneum and posterior rectus sheath, *b*.

RESULTS OF SURGICAL TREATMENT

The results of surgical treatment were analyzed from the standpoint of morbidity, metabolic disturbances, and mortality. They will be discussed in that order.

Morbidity. In the 2 cases in which the cyst was completely excised, the postoperative course was uneventful and the patients were discharged in 2 and 3 weeks, respectively. These cases were considered satisfactory cures.

Cystocholecystostomy was performed in 4 cases, of which 3 made an uneventful recovery. They had an average postoperative hospital stay of 18 days. Follow-up studies were made on these 3 patients. One patient, a 64 year old female, died 1 month after operation of a cerebral hemorrhage. Examination of the cyst at autopsy revealed about 500 cubic centimeters of fluid still present in the cyst which originally contained 2000 cubic centimeters. The second patient who had recovered uneventfully was symptom-free when seen 3 months later. A barium meal at this time

failed to demonstrate the cyst. The third patient in this group was readmitted 5 months later with abdominal pain, tenderness, and fever, but no mass was apparent either on physical or roentgen examination. The patient refused further treatment after 2 weeks and left the hospital with residual tenderness and a low grade fever. The remaining case, one in which the cystocholecystostomy was performed after an unsuccessful marsupialization 3 weeks previously (Case 14, Table II), had a stormy postoperative course. The cyst drained poorly and remained palpable while the patient had a high fever and foul stools. Two weeks after cystocholecystostomy, the cyst was marsupialized again.

The morbidity in the 2 cases where cystojejunostomy was performed was severe. One patient developed a fecal fistula on the tenth postoperative day and died 1 month later of sepsis and debility. The other patient ran a febrile course until he died, 10 weeks after surgery. Autopsy revealed a suppurative pancreatic pseudocyst with a purulent peritonitis and an early malignant cholangioma of the liver.

Marsupialization was associated with a moderate morbidity as evidenced by the summary in Table II. The average duration of the drainage in the 21 patients who survived the procedure was 7.2 weeks. One patient (Case 16, Table II), whose cyst had ruptured preoperatively, developed a postoperative fecal fistula and the drainage persisted for 1 year.

That marsupialization is frequently the safest and most expedient procedure is illustrated by Figures 4 to 10 (retouched photographs). In this case (operated upon by Dr. Peter A. Rosi) complete excision was abandoned for marsupialization because of dense adhesions and adventitious blood vessels. The patient (Case 22, Table II) made an uneventful recovery.

Metabolic disturbances. No evidence of metabolic disturbance was noted in the cases in which the cyst was completely excised or anastomosed to the gall bladder. The deaths which occurred in cystojejunostomy were related to infection and overwhelming sepsis rather than to metabolic causes. That fluid, electrolyte and nitrogen balance can be markedly disturbed in cases in which marsupialization has been performed is evidenced by Case 10, Table II. Detailed data regarding this case are presented to illustrate how profound these losses may be and what measures may be used to overcome them.

TABLE II.—RESULTS OF MARSUPIALIZATION

Patient	Discharged after surgery	Remarks
1. S. H.	Died on P.O. 2	Ruptured cyst
2. S. W.	5 weeks	Slight drainage
3. T. J.	4 months	Healed
4. J. O.	4 weeks	Poor drainage—slight residual mass
5. C. M.	9 weeks	Healed
6. L. G.	5 weeks	Slight drainage
7. F. L.	5 weeks	Slight drainage
8. G. H.	12 weeks	Healed
9. V. R.	2 weeks	Healed
10. F. S.	7 weeks	Healed
11. V. J.	3 weeks	Not recorded
12. D. G.	4 weeks	Slight drainage
13. V. B.	4 weeks	Slight drainage
14. J. N.	3 weeks	Fistula anastomosed to gall bladder
* J. N.	4 weeks	Not recorded
15. L. G.	Died on P. O. 3	Ruptured cyst with peritonitis
16. J. S.	1 year	Ruptured cyst with postoperative fecal fistula
17. V. E.	2 weeks	Not recorded
18. E. K.	2 weeks	Slight drainage
19. V. P.	Died on P. O. I.	Postoperative massive atelectasis
20. L. L.	Died on P. O. 14	Ruptured cyst with peritonitis
21. E. R.	Died 4 months postoperative	Malignant cystadenoma
22. J. W.	4 weeks	Slight drainage
23. F. C.	3 weeks	Slight drainage
24. M. K.	4 weeks	Slight drainage

*Cyst was marsupialized and then the fistula was anastomosed to the gall bladder and then marsupialized again.

This patient was a 49 year old white female who had been struck in the abdomen during an altercation 10 days before her admission to the hospital on August 1, 1945. Following this blow she experienced epigastric pain and vomiting. The patient noted the development of a mass in the left hypochondrium which was verified on physical examination. The abdomen was tender and distended. The

TABLE III.—BLOOD CHEMICAL FINDINGS IN CASE 10

Date	Plasma vol. c.c.	Hematocrit %	Total protein gm. per 100 c.c.	Albumin gm. per 100 c.c.	NPN mgm. per 100 c.c.	Sodium mEq. per L.	Chloride mEq. per L.	CO_2 combining power. c.c. per 100 c.c.	Urine c.c. per 24 hrs.	Cyst drainage c.c. per 24 hrs.	Nitrogen excretion gm. per 24 hrs.
Aug. 10	1470	58	8.13	5.07	129	127	100	50	630	375	5.3
11									650	1200	5.8
12									1600	1300	18.3
13									2730	1000	22.1
14	2083	52	6.66	3.84	55	142	108	58	1350	420	15.0
21	2298	46.5	6.17	4.51	38	143	106	60			

These data were previously published by Dr. W. S. Hoffman, in *Surgical Clinics of North America*. February, 1947, page 217.

red cell count was 3,790,000 and the leucocyte count was 14,500. The urine was scanty and concentrated. No preoperative x-ray films were taken and the preoperative diagnosis was: ruptured spleen. Operation was performed on the day of admission and a large pseudocyst was marsupialized.

Postoperatively a continuous suction apparatus was inserted into the marsupialized cyst to protect the abdominal wall, and drainage from the cyst was collected. In spite of the daily administration of intravenous fluids, on August 10 (10th postoperative day) there was an obvious hemoconcentration, as evidenced by the low plasma volume, and a low serum sodium due to the loss of a large amount of alkaline pancreatic fluid containing sodium bicarbonate. The sodium loss decreased the alkaline reserve and lowered the plasma carbon dioxide combining power resulting in a mild acidosis. The hemoconcentration and low plasma volume caused a retention of nonprotein nitrogen and a prerenal azotemia.

At this point, approximately 7000 cubic centimeters of 0.45 saline in 2.5 per cent dextrose were given during the next 3 days along with liquids and salt orally. On August 14, the plasma volume and serum sodium had been greatly restored by this therapy and in spite of profuse drainage from the cyst, a marked diuresis had been produced which resulted in the excretion of the previously retained nitrogen (Table III). The sodium replacement bolstered the alkaline reserve and elevated the carbon dioxide combining power. At this time, with adequate hydration, the decrease in total plasma protein became apparent and the patient was placed on low protein diet for 7 days to assay the minimal protein requirements. Table IV shows the negative nitrogen balance during the period between August 14 and August 21, which was presumably due to the excretion of previously retained nonprotein nitrogen. On August 21, a high protein diet was instituted. After 14 days, September 4, the plasma volume and the total circulating protein showed remarkable increments and a positive nitrogen balance was reestablished. The patient's clinical improvement closely paralleled the changes in the blood chemistry.

Mortality. The mortality rates are presented in Table V. No deaths occurred in the cases where complete excision or cystocholecystostomy was performed. A 100 per cent mortality rate was associated with cystojejunostomy because of infection in the cyst, leakage at the suture line, fecal fistula, and peritonitis. Four deaths occurred in the 25 cases in which the cyst was marsupialized with a mortality rate of 16 per cent. These cases have been divided into group A, in which the cyst was unruptured preoperatively, and group B, in which the cyst had ruptured preoperatively, and an emergency operation was performed. Of the 21 cases in the unruptured group (A), one surgical death occurred as a result of a massive postoperative atelectasis on the day after surgery (4.8 per cent mortality rate). One patient in this group died 4

TABLE IV.—EFFECT OF HIGH PROTEIN DIET ON CIRCULATING PROTEINS

Date	Diet	Initial Weight kgm.	Weight gain kgm.	Nitrogen balance gm.	Hematocrit level % gm.	Total protein gm. per 100 c.c.	Albumin gm. per 100 c.c.	Plasma volume c.c.	Total circulating protein gm.	Total circulating albumin gm.
Aug. 14	Control	41.4	—	—	52	6.65	3.84	2083	139.6	80.0
Aug. 21	Low	—	6.3	−17.2	46.5	6.71	4.05	2298	155.0	92.9
Sept. 4	High	—	2.7	+225.0	40	6.31	4.51	2865	180.5	131.2

These data were previously published by Kozoll, D.D., Hoffman, Wm. S., Meyer, K.A., and Garvin, T. ,in *Archives of Surgery*, 1946, 53: 683

months after surgery and autopsy revealed a malignant cystadenoma. The 4 cases in the ruptured group (B) had a mortality rate of 75 per cent because of the associated peritonitis and shock.

DISCUSSION

As Archibald and Kaufman stated, it is often impossible to distinguish between a pseudocyst and a true cyst. Since the principles of treatment of a true retention cyst do not differ from those of a pseudocyst, accurate differentiation is not mandatory. However, it is important to differentiate pseudocysts from proliferation cysts and cystadenomas which are neoplastic in character. To this end, all pancreatic cysts should be opened after aspirating the contents, and the interior and lining of the cyst carefully inspected. It is our opinion that these neoplastic cysts should be completely excised where technically possible. On the other hand Carter and Slattery have recommended marsupialization of proliferative cysts to permit destruction of the epithelial lining with radium or sclerosing agents.

The analysis of the mortality rates of the surgical procedures used suggests that complete excision might be the treatment of choice since the morbidity was negligible and no deaths resulted. However, it should be pointed out that complete excision is usually feasible only in the smaller pseudocysts because the larger cysts are fixed by dense adhesions. Judd, Mattson, and Mahorner reported 7 cases in their series of 47 in which cysts ranging from 6 to 10 centimeters in diameter were completely excised. Carter and Slattery recommended complete excision of pseudocysts but in 2 of their cases an opening was inadvertently made in the common duct during dissection of the dense adhesions, and in a third case large adventitious blood vessels on the posterior wall of the cyst caused troublesome hemorrhage from the bed of the pancreas.

Although complete excision is usually reserved for smaller cysts, even in these cases the procedure is not without some hazards. Trauma to the pancreas during the excision of the cyst may cause an acute pancreatitis or a pancreatic fistula. Maingot states the mortality rate of excision of a cyst ranges between 10 and 25 per cent if the cyst is successfully removed. A mortality rate of 55 per cent is given by the same author when an unsuccessful attempt at excision was made.

TABLE V.—MORTALITY OF SURGICAL PROCEDURES

Type of operation	Number of cases	Deaths	Mortality per cent
Complete excision of cyst	2	0	0.0
Cystocholecystostomy	4	0	0.0
Cystojejunostomy	2	2	100.0
Marsupialization of:			
a. Unruptured cyst	21	1	4.8
b. Ruptured cyst	4*	3	75.0

*These cases were published by John Koucky, et al. Surg. Gyn. Obst., 1941, 73: 113.

Cystocholecystostomy, like complete excision, had no immediate surgical mortality associated with it. But, in spite of this, several objections to this procedure present themselves. Incomplete emptying of the cyst was noted in 2 cases. In one of these cases, the patient was reoperated upon and the cyst was marsupialized; in the other case, the patient died of a cerebral hemorrhage a month after surgery and at autopsy, 500 cubic centimeters of bile and mucin were present in the cyst.

The failure of the cyst to empty completely is understandable when one considers that the cyst wall contains no smooth muscle and hence lacks contractile power. It is therefore dependent upon gravity for drainage. Incomplete emptying of the cyst leaves open the possibility of a traumatic rupture of the cyst with its attendant high mortality. A further objection to the creation of a large diverticulum of the biliary system by this procedure is the stasis of bile with activation of the enzyme lipase and subsequent fat necrosis. This last objection could be overcome, as one of us (KAM, 24), suggested in an earlier paper, by using the technique of Walzel, in which a complementary ligation of the cystic duct is performed.

Since biliary tract disease is frequently associated with pseudocysts, a Graham-Cole gall bladder visualization should be performed to determine the function of the gall bladder in those cases in which a cystocholecystostomy is contemplated.

Cystojejunostomy was performed in 2 cases in this series with death occurring in both cases. Better results with this procedure were obtained by Adams and Nishijima who reported its successful employment in a pseudocyst and also in a papillary cystadenoma, where it served as palliation. Follow-up studies on these 2 patients 3 months later revealed them to be symptom-free and when a barium meal was given, no barium entered either of the cysts. When a postoperative barium meal was given to one of our patients who ran a septic course after a cystojejunostomy, the barium did enter the cyst. Subsequent autopsy of this patient showed a suppuration in the cyst and peritonitis. This evidence suggests that the creation of a large jejunal diverticulum, into which food can pass and accumulate, is potentially dangerous. An additional hazard in cystojejunostomy is leakage at the suture line which occurred in our second case and caused a fecal fistula and death from peritonitis. Finally, the ability of enterokinase and bile to activate the pancreatic enzymes trypsinogen, chymotrypsinogen and lipase, may cause acute pancreatitis, and fat necrosis.

Marsupialization in our series was performed with a low mortality rate (4.8%) in the unruptured cysts. This compares with the 7.6 per cent mortality reported by Babcock. One of the objections raised to marsupialization is the development of persistent fistulas which occur in 15 per cent of cases according to Babcock. In our cases the drainage persisted for an average of 7.2 weeks and no persistent fistulas developed in so far as the follow-up study could ascertain.

A persistent fistula, if it should develop, may be treated by medical or surgical measures. Among the medical measures employed, Comfort, Osterberg, and Priestley reported that ephedrine sulfate, ¾ grain, given subcutaneously before a meal reduces the volume of secretion from a pancreatic fistula by 50 per cent. The concentration and total bicarbonate and total output of lipase were also reduced while amylase was not affected. They also noted that atropine sulfate, 1/75 grain, given subcutaneously before a meal reduces the volume of fistula secretion by reducing gastric motility and secretion and thus indirectly decreasing the secretion liberated. Craft stated that ephedrine sulfate, like epinephrine, decreased pancreatic secretion by its vasoconstrictive action on the pancreatic arterioles.

Other nonoperative measures in the treatment of a pancreatic fistula are based on the use of irritants to cause the proliferation of granulation tissue with eventual fibrosis of the fistulous tract. In this connection, Judd (16) stated that the absence of an epithelial lining in the cyst favored the formation of granulation tissue in response to irritants. Sodium morrhuate packs were placed in a marsupialized cyst by Gordin with complete healing in 18 days. Radium was used by Hamilton without marked improvement in the fistula. Roentgen therapy was used successfully by Culler in 2 cases of persistent fistula. Maingot states that if the fistula does not close within 6 weeks, and most fistulas do tend to close spontaneously, operation should be advised. The operative treatment of persistent fistula, as reported by Lahey (1, 21), is the transplantation of the fistula into the jejunum. Maingot states that this is a relatively safe surgical procedure as evidenced by the 3.8 per cent mortality in the 26 cases of pancreaticojejunostomy and pancreaticogastrostomy collected and reported by Lahey.

The postoperative care of a patient with a marsupialized cyst requires special attention to fluid, electrolyte, and nitrogen balance. As Case 10 Table II illustrated, the fluid and electrolyte loss may be so great as to produce a state of hemoconcentration with azotemia and acidosis. This may be accompanied by a profound protein loss and a negative nitrogen balance. The replacement of the fluids, electrolytes and protein with the re-establishment of a positive nitrogen balance indicates that these occasional complications can be successfully combatted, even when severe, if they are recognized early and treated vigorously. These postoperative measures have greatly reduced the hazards which formerly attended marsupialization in some instances. A further adjunct to postoperative care is the use of bronze or aluminum paste on the skin and continuous suction in the cyst to prevent the drainage fluid from excoriating the skin.

Ruptured pseudocysts have a mortality rate of 75 per cent, largely because of the resulting peritonitis and shock. This alarming mortality rate emphasizes the importance of early, elective surgical intervention in pancreatic pseudocysts to preclude the possibility of rupture of the cyst.

SUMMARY

1. A report is given of 31 cases of pseudocysts of the pancreas, which were treated surgically.

2. Severe, blunt abdominal trauma was an etiological factor in 51.6 per cent of cases; cholecystitis, cholelithiasis, and pancreatitis were factors in 16.1 per cent of cases.

3. The amount of fluid found in the cysts ranged between 15 and 7000 cubic centimeters and averaged 2686 cubic centimeters.

4. In 13 of 14 cases in which a barium meal was given displacement of the stomach was shown and in 6 of 7 cases in which a barium enema was given displacement of the transverse colon was shown where these procedures were utilized.

5. Complete excision of a small pseudocyst was done in 2 patients without a mortality. Cystocholecystostomy was performed in 4 patients without a mortality. Marsupialization was performed in 21 unruptured cysts with a mortality rate of 4.8 per cent and in 4 ruptured cysts with a 75 per cent mortality rate. Cystojejunostomy was performed in 2 cases with a 100 per cent mortality rate.

6. Following marsupialization in 1 patient, profuse drainage from the cyst caused hemoconcentration, mild acidosis, azotemia, and a negative nitrogen balance. Energetic administration of fluid, electrolytes, and a high protein diet corrected these complications.

7. The average duration of drainage from the cysts following marsupialization was 7.2 weeks and, in no instance, did a persistent fistula develop.

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ENDOMETRIOSIS—ITS SURGICAL SIGNIFICANCE

A Critical Analysis of 179 Cases

FRANCIS J. KELLY, M.D., Amarillo, Texas, and K. RAMSAY SCHLADEMAN, M.D., Fort Wayne, Indiana

ENDOMETRIOSIS is generally considered to be a lesion containing ectopic uterine mucosa.

Many authors recently have confined their remarks to the extrauterine manifestation and for this reason it was felt worth while to study the problem in its entirety rather than limit our considerations. Though cognizant of the very probable difference in origin of the two types (intrauterine and extrauterine), we were especially interested in two factors which could be affected by endometriosis regardless of location. One is the too infrequently emphasized symptom of progressive dysmenorrhea and the second is the incidence of absolute fertility following conservative surgical management as determined by careful follow-up study.

In 1896 von Recklinghausen enunciated his theory of misplaced derivatives of the wolffian or muellerian duct, which might explain the presence of ectopic endometrium. Cullen's monumental work in 1908 followed, but it was not until 1921, subsequent to the excellent study of Sampson (15), that the lesion became of widespread clinical significance. At the present time there remain many theories concerning the origin of endometriosis, no one adequately explaining the diverse manifestations. It is increasingly evident that the disease may be due to several factors. The most widely accepted suppositions include the following:

1. The embryonic theory, oldest of all, is based on the fact that the epithelium of the pelvic peritoneum, fallopian tubes, uterus and germinal epithelium of the ovary have a common origin in the celomic epithelium and under certain conditions the embryonic rests contained in the pelvic peritoneum reproduce endometrium.

2. The metaplasia theory attempts to explain endometriosis by holding that the peritoneum is stimulated to form glands resembling endometrium. The greatest objection to this very convenient explanation is the necessity of assuming metaplasia.

3. Sampson's (16) view, and perhaps the most widely known, postulates that endometrial cells escape, by way of the fallopian tubes, at menstruation and are deposited on the ovary or pelvic peritoneum and develop as an implant. The chief objection to this theory is its failure to explain extraperitoneal lesions, in the bladder, inguinal glands, or as seen from 1 case in this series, in the umbilicus.

4. Recently there has been renewed interest in lymphatic transportation as advanced by Halban in 1924. Sampson (17) in 1927 demonstrated endometrial fragments in the veins of the uterus.

5. Finally, surgical implants are occasionally seen following pelvic operations and one such instance is reported in the present series.

From the Departments of Surgery and Pathology, Scott and White Clinic, Temple, Texas.

Dr. Kelly is chief surgeon, Veterans Administration Hospital, Amarillo.

MATERIAL

During 1,991 consecutive abdominal gynecologic operations at Scott and White Clinic, 179 (8.9 per cent) histologically verified cases of endometriosis were found; and these, together with follow-up study, form the basis for this paper. The average age of these patients was 38 years, the youngest 20, and the oldest 65 years.

Fallas and Rosenblum report 1.62 per cent endometriosis in 15,975 gynecologic laparotomies done in two Los Angeles private hospitals between 1930 and 1939. Sanders encountered the lesion in 17 per cent of 700 laparotomies for gynecologic diseases. Meigs (12), on the other hand, found that 28 per cent

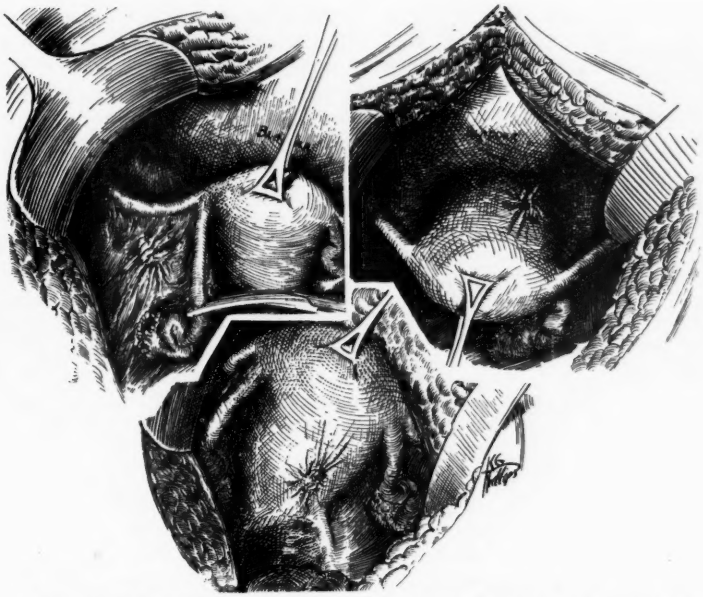

Fig. 1. Multiple sites of implantation as seen at operation. Note typical puckering and dense, solid strands.

of 400 private patients and 5.8 per cent of 400 patients at the Massachusetts General Hospital showed extrauterine endometriosis microscopically. It is difficult to determine the incidence of endometriosis as many of the tumors are small and easily overlooked in routine examinations due to the multiplicity of sites of invasion (Fig. 1). The serious consequences of the unrecognized tumor requires no elaboration and it becomes imperative for the surgeon to search carefully and to recognize the characteristic bluish-black dots on the pelvic peritoneum.

APPEARANCE

Endometriosis presents a rather typical gross appearance, best referred to as "puckered" areas, especially in the advanced stages. Early manifestations are likewise characteristic in their "blueberry spot" form. When these cysts perforate or are ruptured, a black, tarry, irritating fluid may be scattered over the contiguous organs. Just as the cysts react to ovarian stimulation at the menstrual phases much the same as normally situated endometrium, so at the menopause, whether natural or artificial, endometrial lesions will recede.

The presence of adhesions due to endometriosis are frequent and when once seen should rarely be confused with those caused by other pelvic inflammatory disease. The adhesions of the latter are generally broad and labile and easily torn while those of the former are tough and solid with a tendency to strand formation. Fixed retroversion of the uterus should always cause the surgeon to suspect endometriosis. Chocolate cysts of the ovary are less likely to be overlooked, however, we believe that it is imperative that a microscopic section be performed at once if radical surgery is contemplated to exclude simple hemorrhagic cysts.

PATHOLOGY

The microscopic picture of extrauterine endometriosis is that of well defined endometrial glands surrounded by endometrial stroma varying in amount from little or none to a definitely stromal collar. Those implants influenced by hormones contain extravasated blood and hemosiderin laden phagocytes.

TABLE I.—SYMPTOMATOLOGY

		No. of cases	Percentage
Acquired dysmenorrhea		86	48.2
Severe	24		
Moderate	37		
Mild	25		
Increasing dysmenorrhea		60	33.5
Menorrhagia		45	25.1
Low backache		31	17.3
None		25	13.9
Headache		18	
Nervousness		17	
Gastrointestinal disturbance		16	
Dyspareunia		15	
Irregular periods		15	
Metrorrhagia		13	
Abdominal mass		11	
Referred pain		6	
Rectum	2		
Stomach	1		
Thigh	1		
L.L.Q.	1		
R.L.Q.	1		
Urinary frequency		6	
Menopause		6	
Weakness		2	
Premenstrual discomfort		2	
Painful scar with menstruation		1	

The microscopic picture of intramural endometriosis or adenomyosis consists of well defined epithelial islets surrounded by varying amounts of stroma within the myometrium. Serial study of such implants will show them to be continuous with the endometrium and the formation is that of a crypt-like structure extending into the myometrium (1, 13). The "adenomyoma of Cullen" is a variant of intramural endometriosis in which the epithelial implants are incorporated in a leiomyoma.

The diagnosis of adenomyosis in this series was based on the finding of endometrial inclusions in the myometrium, a distance of at least the diameter of a full low power field from the base of the endometrial lining of the uterine cavity. Serial study would undoubtedly have shown these areas to be distal prolongations of cryptic invaginations from the endometrium.

SYMPTOMATOLOGY

The clinical diagnosis is admittedly difficult because of the variable history, symptoms, and physical findings. There is one symptom, however, toward which particular attention was directed in this review. This is the factor of increasing or progressive dysmenorrhea. Though King and Fiddes, in 1929, pointed out this symptom as being characteristic, the majority of writers on this subject, we feel, do not emphasize this factor sufficiently. We agree with Fallon, Brosnan, and Moran that, when present, the symptom should be considered pathognomonic. In a review of 200 articles, these authors found only 12 who emphasized this symptom.

As noted in Table I, 1 out of 3 patients complained of increasing dysmenorrhea. This takes on added significance when it is noted that only 48.2 per cent complained of the repeatedly emphasized symptom of acquired dysmenorrhea, which, though important, is part of the symptom complex of many disorders of the female genital organs. The distinction is important and should not be confused.

With a complaint of painful periods it should be determined whether or not the dysmenorrhea has been present since menarche or has been acquired following normal menstrual cycles. In most cases of endometriosis, the latter situation will have prevailed. If the patient further states that her dysmenorrhea, acquired or not, has progressively become more intense with each succeeding cycle, the diagnosis rests with endometriosis. We know of no other condition in which this symptom is present. The rate of progression is variable and many patients take several years before the severity increases sufficiently to bring them to their physician. On the other hand, the patient may have had painless periods for years, may develop dysmenorrhea which becomes more intense with each succeeding period, and may require treatment within a very few months from the initial onset. Too, the length of time the patient may complain of pain during each period will vary, though as a rule the longer the duration of progression the more extended will be the dysmenorrhea at any particular period. In several instances patients were without pain for only a few days in each complete cycle.

One out of 4 complained of an increased amount of flow at the menstrual period. Low backache was a relatively frequent complaint during menses, though in no appreciably greater incidence than that found in the average female with pelvic complaints. Twenty-

TABLE II.—CLINICAL DIAGNOSES

	No. of cases	Percentage
Uterine displacement	131	73.2
Uterine leiomyoma	90	50.3
Adhesions	45	25.1
Ovarian cyst	39	21.8
Endometriosis	26	14.5
Pelvic inflammatory disease	21	11.7
Psychoneurosis	8	4.5
Appendicitis, recurrent	7	
Ectopic pregnancy	2	
Essential dysmenorrhea	2	
Menopause	2	
Cancer of uterus	2	
Cystitis, duodenal ulcer, urethritis, cancer of sigmoid, urachal cyst, intestinal obstruction, pyometritis, incarcerated omentum	1 each	

five patients, on the other hand, gave no symptom referable to menstruation.

Thirty-two patients (17.9 per cent) had lesions of the rectosigmoid (Fig. 2), but only one-half of these gave a history of gastrointestinal disturbance. One of these, however, had a partial intestinal obstruction while the remainder complained of painful defecation, abdominal distention or flatulence immediately prior to or during the menstrual period. Masson found endometriosis of the sigmoid and rectovaginal septum in 34 of 576 cases or in 5.9 per cent while Sanders found that 12 per cent had involvement of the sigmoid.

Dyspareunia was a complaint of 15 patients and this, of course, must be considered in the high rate of relative sterility in this group of patients.

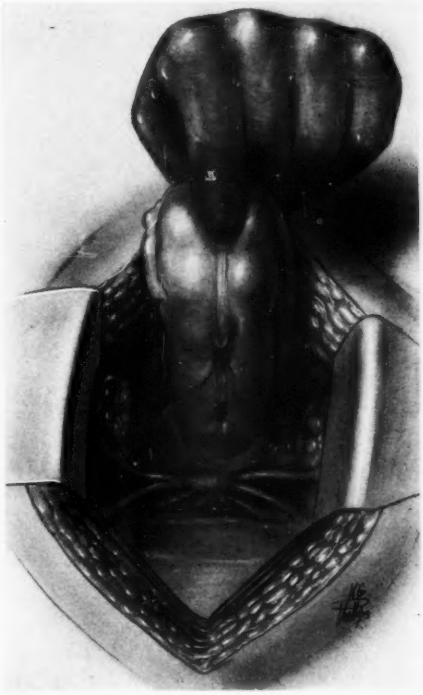

Fig. 2. Characteristic appearance of endometriosis on the sigmoid. The uterus has been removed.

DIAGNOSIS

It is a regrettable fact that endometriosis, in spite of its prevalence and importance, has a low diagnostic index. In this series the diagnosis was correctly made in 14.5 per cent. In this connection it is to be noted that had the symptom of increasing dysmenorrhea been regarded as indicative of endometriosis, as we now believe it should be, the diagnostic index would have more than doubled to 33.5 per cent—the percentage of patients with this complaint. Uterine displacement (prolapse, retrocession, retroversion) is a common finding in the presence of endometriosis, often due to the inflammatory reaction and subsequent adhesions, induced by the peritoneal implants. A fixed retroversion should at once cause the physician to consider endometriosis. A summary of the clinical diagnoses made in this series is presented in Table II.

LOCATION OF ENDOMETRIOSIS

Endometriosis is extremely rare above the umbilicus. In this series 1 endometrioma was found in the umbilicus. The distribution of the lesions follows that found in most large series (Table III). The peritoneal surface of the uterus was the most common site, the lesion being present in 64 patients. The wall of the uterus was next in frequency, with 46 patients having diffuse adenomyosis and 11 found to have intrauterine endometriomas. The cul-de-sac was involved in 42 patients and in most cases the result was a marked retrodisplacement. Situations where heterotopic endometrium was found in the group of patients included in this study are consolidated on the illustration in Figure 3.

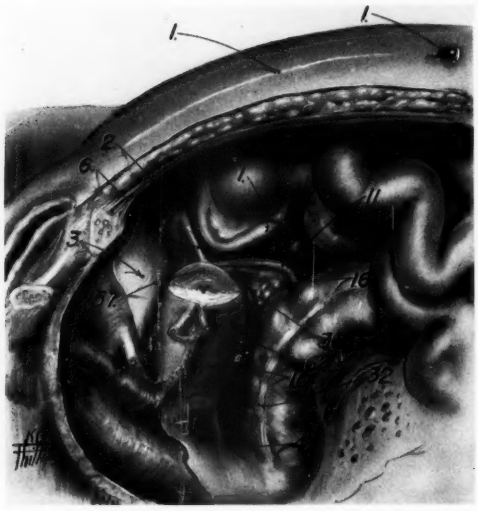

Fig. 3. Distribution of ectopic uterine mucosa in this series. The arrows indicate the sites of invasion. The figures indicate the number of cases in which the lesion was found in each location (Table III).

In 1 patient the lesion was found in a laparotomy wound. Keene and Kimbrough found 1 in this location in a series of 118 cases, while Jenkinson and Brown reported 3 in 117 cases. In our group, 81 patients had been subjected to a previous abdominal gynecologic operation. It is evident then that manipulation or trauma of the pelvic organs at the time of surgery can be a direct etiologic factor in the spread of endometriosis. That the original production of endometriosis can be influenced by manipulative procedures must be considered, for in this series a relatively large number of patients had undergone previous surgery (45.3 per cent). The average number of years since that surgery was 8.4 years.

ASSOCIATED PELVIC CONDITIONS

A characteristic feature of endometriosis is the frequent occurrence of pathological conditions in association with the lesion. Displacement of the uterus was relatively common, particularly retroversion (Table IV). One hundred and forty-eight patients had some type of displacement not considered normal. Leiomyoma occurred in 88 (49.4 per cent) of 178 patients (1 previous hysterectomy). Counseller reported 54.5 per cent of 308 patients and Keene and Kimbrough found 55.4 per cent with myoma. Two patients in our group had endometriosis concomitant with adenocarcinoma of the uterus. An interesting finding, in view of the relative sterility of the patient with endometriosis, was 1 patient in whom the lesion was found during surgery for tubal pregnancy.

TABLE III.—LOCATION OF ENDOMETRIOSIS

	No. of cases
Surface of uterus	64
Mural	57
Diffuse	46
Endometrioma	11
Cul de sac	42
Surface of ovary	38
Rectosigmoid	32
"Chocolate" cyst of ovary	16
Surface of bladder	13
Fallopian tube	11
Broad ligament	10
Round ligament	6
Parietal peritoneum	2
Appendix	1
Umbilicus	1
Abdominal scar	1

SURGICAL PROCEDURES

The choice as to the correct type of operation to be employed is not always clearly defined. The extent and location of the lesions are of primary consideration though the age of the patient is a factor, especially in those over 40 years. The problem, however, will always be present as endometriosis is not a disease of old age but rather a disease affecting a large percentage of women during their reproductive life. Most surgeons are in agreement with the statement that it is well worth while to spend 30 minutes or more if necessary, excising individual lesions than to perform the more radical procedures. That this conservatism, when possible, will bear fruit will be shown later (Table VI).

In our series it was necessary to do the more radical procedures in 132 patients. One hundred and thirty of these required hysterectomy (72.6 per cent) while the remaining 2 patients were treated by bilateral oophorectomy alone.

As might be expected with these lesions, lysis of adhesions of more than minor nature was performed in a relatively large number of cases (36.9 per cent). It is not surprising then

TABLE IV.—OPERATIVE FINDINGS

	No. of cases	Percentage
Displacement of uterus		
Retroversion (with or without prolapse)	92	51.4
Prolapse and (or) retrocession	54	30.2
Anterior	14	
Suspension	3	
Antiflexion	2	
Previous hysterectomy	1	
Not known	13	
Associated pelvic disease		
Fibromyoma	88	49.4
Adhesions	75	
Chronic salpingitis	41	
Ovarian cortical fibroma	8	
Atrophy of tube and ovary	5	
Adenocarcinoma of uterus	2	
Tubal pregnancy	1	
Cysts of ovary		
Follicular	97	
Hemorrhagic	68	
Corpus luteum	15	
Hemorrhagic cystadenoma	6	
Dermoid	1	

to find that of the 48 patients in whom hysterectomy had not been performed, all but 1 required uterine suspension (Table V).

No patient received presacral resection, though occasionally considered, as the experience at this clinic has been that surgical replacement of the uterus has satisfactorily relieved the symptoms arising from displacement.

FERTILITY

Perhaps the most important factor in a discussion of endometriosis is its relation to fertility, both prior to and following surgery. This is of special consideration to the patient in the child-bearing age. If conservative surgery is to be practiced, what chance will the patient have of becoming pregnant following conservation of the reproductive organs? We believe it is sufficient to warrant the plea to err on the side of conservatism rather than to employ specific treatment and destroy ovarian function at the time of surgery.

If symptoms persist, the diagnosis having been made, roentgen therapy may then be applied to one or both ovaries. In our series this has been necessary in 7 patients with relief of symptoms in all cases.

Most observers conclude that 10 to 15 per cent of marriages do not result in pregnancy. Reynolds and Macomber stated that the per-

TABLE V.—MAJOR OPERATIVE PROCEDURES

	No. of cases	Percentage
Hysterectomy	130	72.6
Hystero-oophorectomy	113	
Supracervical	15	
Total	2	
Freed adhesions	66	36.9
Uterine suspension	47	26.3
Unilateral oophorectomy	26	14.5
Bilateral oophorectomy	2	
Excision of umbilicus	1	
Release of obstruction	1	

centage of sterile marriages in Massachusetts was not lower than 10, and probably not higher than 13 per cent. In this study we have used the figure of 88 per cent as representing normal fertility.

Under the heading of absolute fertility are included only those patients who had actually been pregnant prior to surgery. Those patients, however, married less than an arbitrary 5 year period prior to treatment were excluded. Thus, it was determined that of 166 patients, only 46.4 per cent had ever become pregnant. Jenkinson and Brown found 41 per cent had been pregnant; Keene and Kimbrough reported 59.1 per cent, while Meigs (12) found 65.7 per cent fertility.

The relationship between endometriosis and delayed or infrequent childbearing is well known. Cause and effect, however, have yet to be adequately defined. Certainly, as Meigs (11) has stated, "women with a stigma of underdevelopment (and many of these do not marry because they are also underdeveloped sexually) and well developed women who put off marriage too long or who try to put off pregnancy until well after married life has begun are likely to develop endometriosis." On the other hand, the presence of endometriosis may result in marked retroversion, dyspareunia, pelvic inflammation and intrauterine endometrioma which in themselves are not

TABLE VI.—RELATION OF ENDOMETRIOSIS TO PREGNANCY

Average age (all patients)	38 years
Normal fertility	88 per cent
Absolute fertility in this series (excluding those married less than 5 years)	46.4 per cent*
No. of patients relatively fertile following surgery	38
Average age	31 years
Absolute fertility (following surgery)	23.7 per cent

*166 patients.

infrequent causes of relative sterility. Of the 166 patients who had been pregnant prior to surgery the average interval between their last pregnancy and the time of operation was 11 years. Keene and Kimbrough reported the average interval of sterility in 39 patients was 9.5 years.

Following surgery 38 patients in this study could be classed as relatively fertile; that is, pregnancy was both theoretically and practically possible as far as could be determined. The average age of this group of patients was 31 years. It has been possible to follow these patients a minimum of 2 years and a maximum to date of 6 years. Though a longer follow-up interval would be desirable, the results during this time serve to re-emphasize the value of conservative surgery whenever possible. Eleven pregnancies have occurred in 23.7 per cent of these 38 patients and all occurred within 4 years following surgery. Two patients have been pregnant twice during this time, neither of whom had previously been pregnant.

SUMMARY

1. A brief résumé of the most widely accepted hypotheses concerning the etiology of endometriosis is presented. It is evident that no one theory adequately explains the variable manifestations.

2. Endometriosis was present in 8.9 per cent of 1991 consecutive gynecologic laparotomies.

3. Progressive dysmenorrhea, when present, is pathognomonic of endometriosis. If more attention were directed toward this symptom the low diagnostic index now prevalent could be appreciably raised.

4. Though radical operative procedures were considered necessary in the majority of these patients, conservatism, when possible, is justified, as indicated by an absolute fertility of 23.7 per cent after conservative surgery had been carried out.

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THE ETIOLOGY OF STRESS INCONTINENCE

S. RICHARD MUELLNER, M.D., Boston, Massachusetts

THE precise etiology of exertional incontinence has to date remained obscure. Opinions are still divided on the nature of the lesion responsible for the impaired urinary control. Most authors ascribe stress incontinence to traumatized urethral sphincters as a result of childbirth; others insist that it is caused by obstetrical injury of the bladder supports.

In a previous investigation (4) 95 patients with exertional incontinence and 45 continent multiparas were carefully studied by cystometry, cystoscopy, cystography, and urethrography.

These studies failed to reveal a specific lesion of stress incontinence, but made it clear that unless much more was known about the normal mechanism responsible for urinary control, the cause of exertional incontinence could not be detected. Specifically, one had to know how a normal woman initiated and shut off her urinary stream.

This information could not be obtained by cystometry or cystography and urethrography. It was therefore necessary to devise a technique of study which could portray the dynamic events of micturition.

Direct observation of the bladder under the fluoroscope seemed to offer such a possibility, and for the past year and a half a study of normal and abnormal micturition in men, women, and children was carried out at the Beth Israel Hospital (5). A total of 85 observations have been made to date, 30 of these were of women suffering from stress incontinence.

The technique of study was briefly as follows: The bladder was first filled through a No. 16 French catheter with a contrast medium consisting of a 5 per cent (5%) solution of sodium iodide to which a 20 cubic centimeter ampule of aqueous diodrast (35% by volume) had been added. The catheter was then withdrawn. A filling of the bladder with 200 to 250 cubic centimeters of this mixture was usually sufficient for study in the average case.

From the Department of Urology, Beth Israel Hospital, Boston.

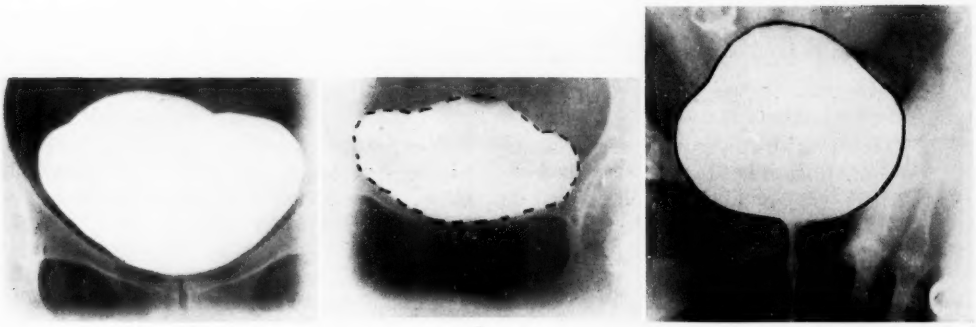
Observations were made with the subject supine, standing, and turned to one side or the other. Care was taken to maintain the relationship of the x-ray tube to the symphysis pubis, so that changes in the position of the bladder resulting from a change of posture could be accurately evaluated.

The effects of coughing and straining on the bladder and on its supports and the events at the beginning of micturition and when the urinary stream was inhibited were then carefully observed. Spot films of the bladder while the patient was in various positions and during micturition were taken from time to time.

A special plastic urinal (Fig. 1) which would not cast an x-ray shadow was devised to permit the subject to void while standing.

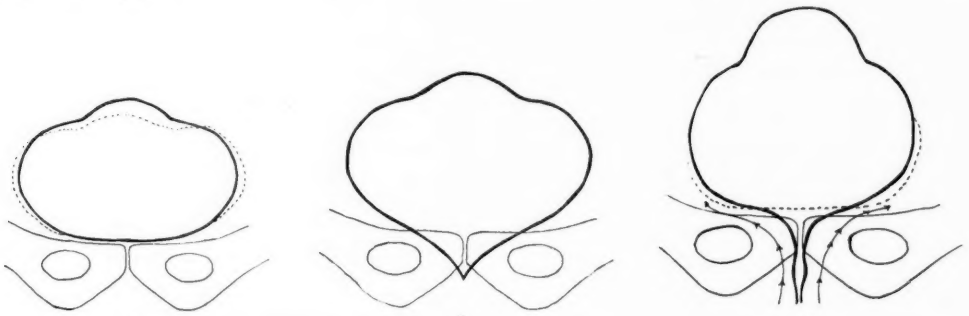
The precise pathology of exertional incontinence became apparent when the findings in the normal nullipara and in the continent multipara were compared with the observations in women with stress incontinence.

Fig. 1. Plastic urinal. Note long handle.



a b c

Fig. 2. a, C. M., nullipara, Recumbent; note shape of the bladder base and its position in relation to symphysis pubis. b. Erect; note that bladder position is maintained in erect posture. c, During micturition; the vertical diameter of the bladder is increased, and the horizontal diameter has decreased. The internal sphincter occupies a somewhat lower position in the pelvis.



a b c

Fig. 3. a, Diagram of bladder in a nullipara. Dotted line shows change of bladder shape on coughing. Note that bladder base remains steady. b, Note "pointed" appearance of bladder base and descent of internal sphincter with voluntary attempt at micturition. c, Voluntary inhibition of the urinary stream. Arrows point to the direction in which the bladder base is lifted up to shut urinary stream off. Dotted line shows bladder shape when urinary stream is stopped.

In the normal nullipara while recumbent, the bladder has a smooth outline and its base lies just above the symphysis pubis (Fig. 2). This position of the bladder is maintained when she stands up. On coughing, the bladder base does not yield, but the impulse from the increased intra-abdominal pressure is dissipated along the dome and to the sides of the bladder, revealing the excellence of the bladder supports (Fig. 3a).

When she is asked to void, the bladder base can be seen to descend sharply, so that the region of the internal sphincter becomes the most dependent portion of the bladder and assumes a "pointed" appearance (Fig. 3b). This is the first important maneuver in the complex process of micturition, and its significance was neither known nor appreciated in the past. It is this descent of the internal sphincter which opens it slightly and permits a small amount of the contrast medium to enter the proximal urethra. This is followed by contraction of the detrusor, and uninterrupted micturition then ensues. Once micturition has begun the bladder base returns to a position slightly lower than that of its resting phase (Fig. 2c).

If the subject is now asked to inhibit the urinary stream she pulls the bladder base up quickly and to a level slightly higher than it had assumed before micturition. The bladder base becomes horizontal, and the urinary stream is promptly shut off (Fig. 3c).

In the continent multipara the events are very similar, except that the bladder is some-

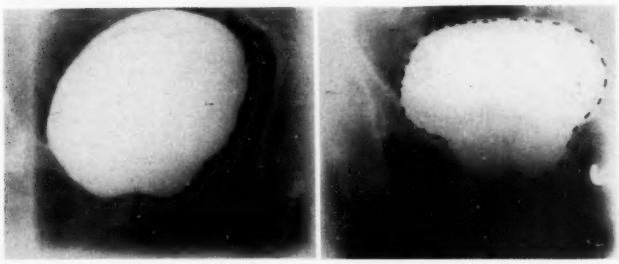


Fig. 4. a, left, R. G., continent multipara, recumbent. b, Erect; note descent of bladder base, indicating laxity of general bladder supports, yet not causing stress incontinence.

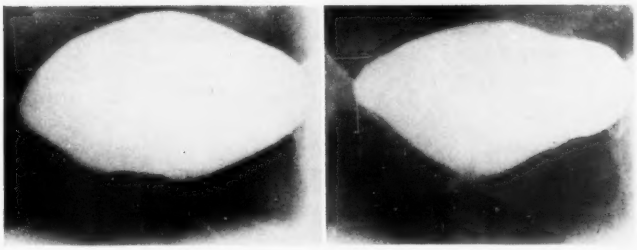


Fig. 5. a, left, A. H., multipara, stress incontinence. Recumbent; note position and shape of bladder base. b, Erect; note "pointing" of bladder base. Internal sphincter has descended. "Pointed" bladder base is typical of stress incontinence.

what larger and flabbier and the bladder supports are more yielding. The bladder base sinks to a considerably lower position in the standing as compared to the recumbent posture (Fig. 4a and b).

On coughing or straining the bladder base descends as a whole with the sudden increase in intra-abdominal pressure. These women clearly demonstrate that mere relaxation of the bladder supports does not impair urinary control.

A few points in the observations of women who can control the urine deserve emphasis.

First, the bladder base, and especially the region of the internal sphincter, is in close relationship to the muscles of the pelvic floor. Second, these muscles play a very active part in the initiation and in the inhibition of the urinary stream. Third, when the continent woman stands up, these muscles form a firm support for the internal sphincter and not only take on the added gravitational strain induced by the erect posture which amounts to 10 to 12 millimeters of mercury (6) but they also take up any additional sharp increases in intravesical pressure which result from exertion, coughing, or sneezing, and thus protect the internal sphincter against these stresses.

A review of the anatomy of the muscles of the pelvic floor and especially the contributions made by Thompson, Savage, Holl, Lesshaft, and Smith make it clear that it is the pubococcygeus portion of the levator ani and, perhaps to a very much lesser extent, the deep transverse perinei muscle which play this important part in micturition and in urinary control. These muscles, with a somatic innervation, are responsible for the descent of the internal sphincter at the start of micturition, and they sharply lift the bladder base up to shut the stream off. It is the descent and the opening of the internal sphincter which initiates the reflexes of micturition.

Under the fluoroscope the descent and the "pointing" of the internal sphincter appear as a downward pull. Actually, there are no mus-

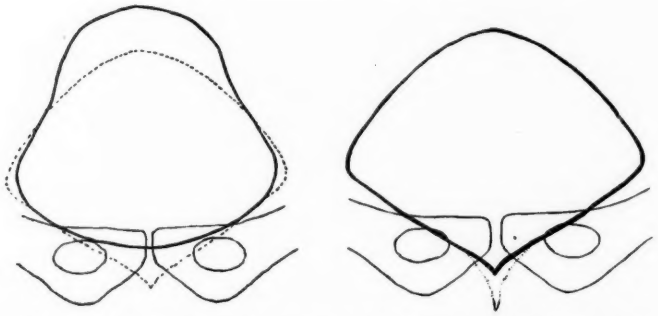


Fig. 6. a, left, Diagrammatic representation of stress incontinence. Solid line, bladder during recumbency. Dotted line, "pointing" of bladder base and descent of internal sphincter when erect. b, Solid line, bladder during erect posture. Dotted line, showing minimum descent of internal sphincter which is necessary for micturition.

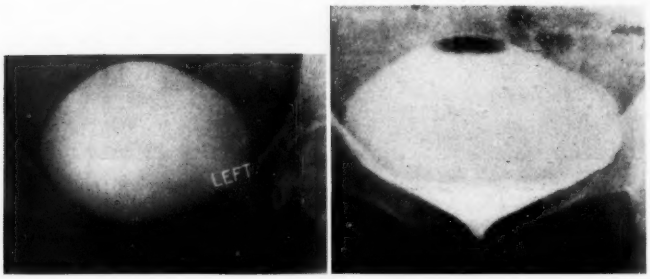


Fig. 7. a, left, I. G., primipara, life-long stress incontinence unaffected by birth of child. Recumbent; note smooth bladder base above symphysis. The internal sphincter is normally shut off. b, Erect, not straining; note "pointing" of bladder base and "funneling" of internal sphincter, revealing its congenital weakness.

cles in the pelvic floor or in the perineum which could pull the bladder base down. It is more correct to speak of this maneuver as a "downward push" and it is brought about by the joint forces resulting from the increased intra-abdominal pressure (the fixation of the diaphragm at the end of a brief inspiration and the contraction of the abdominal muscles), gravity, and the relaxation of the muscles of the pelvic floor (3).

In contrast to animals, only erect man has a pelvic outlet which is constructed to cope with the problem of gravity resulting from postural changes.

Erect man thus has a dual mechanism for urinary control. First, there is the internal sphincter which, in tonic contraction while the detrusor is relaxed, effectively shuts the bladder off, and second, the muscles of the pelvic floor. For urinary control in the female, the distal two-thirds of the urethra are of no consequence, since this much of the urethra can be excised as it usually is for carcinoma of the urethra, without in any way impairing urinary continence (2, 10).

If these important facts are kept in mind, the lesion of exertional incontinence becomes at once apparent.

While recumbent, women with stress incontinence have a bladder shape very much like that of the continent multipara. On coughing, the bladder base makes a considerable excursion downward, but the region of the internal sphincter takes up most of this downward thrust and yields even more than the base.

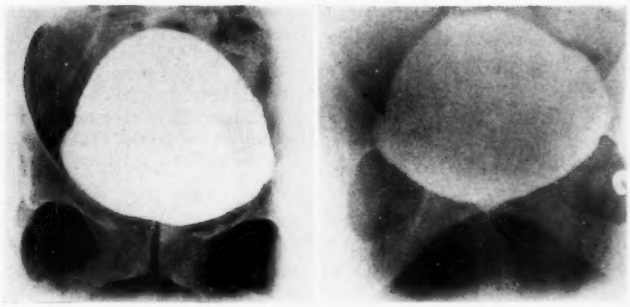


Fig. 8. a, left, S. G., nullipara, life-long stress incontinence. Recumbent; note smooth bladder base. Internal sphincter shut off normally. b, Erect; arrow points to "funneling" of internal sphincter.

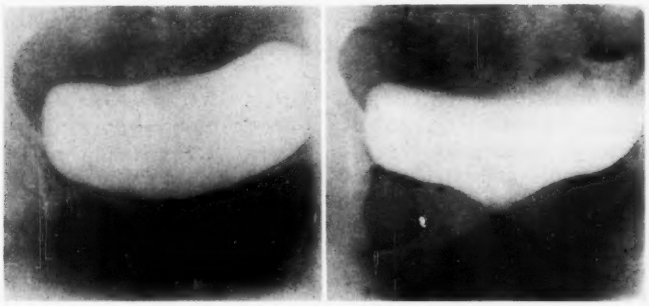


Fig. 9. a, left, S. H., nullipara who developed stress incontinence after a recent hysterectomy. Recumbent; note smooth bladder base. Internal sphincter is normally shut off. b, Erect; note pointed bladder base and descent of internal sphincter.

While lying quietly the internal sphincter is shut off normally, showing no evidence of injury or deficiency (Fig. 5). When the patient is now made to stand up, the bladder assumes an appearance which has been present in every case of incontinence, studied by means of this technique, and one which can therefore be said to be typical of stress incontinence (Fig. 5b). While the bladder base descends as a whole in the erect as compared to the recumbent position, it is specifically the region of the internal sphincter which descends most and becomes the most dependent portion of the bladder. The bladder base assumes the "pointed" appearance, characteristic of the bladder poised for micturition. It then takes only very little further descent to open the internal sphincter and to allow a jet of urine to escape. This then is an altogether different base line than the one which is seen in the continent nullipara or multipara, and it is obviously brought about not by a general inadequacy of the bladder support but by a very particular one. In exertional incontinence it is precisely the region of the internal sphincter which is not supported and which permits this sphincter to become dependent, so as to give the bladder base its characteristic appearance when the patient stands up. It is for this reason that most women with stress incontinence do not lose their urine when recumbent but lose it when they suddenly increase the intra-abdominal pressure while they are up and about.

It has been common experience that women with severe incontinence are apt to lose their entire bladder contents with the initial stress. The fluoroscope reveals why this is so. The supports of the internal sphincter in these

women do not have enough tonicity to pull the bladder base up all the way and to level it off in order to inhibit the urinary stream, and since these women fail to lift the bladder base up sufficiently high micturition goes on to completion once it has ensued.

Exertional incontinence in nulliparous women has always been puzzling. Two such cases were studied fluoroscopically, and the particular cause of stress incontinence in these women also could be demonstrated. In both women the internal sphincter was perfectly normal when they were lying down (Figs. 6 and 7). When they were made to stand up, the bladder base was still well supported, but the internal sphincter now formed a deep dimple, demonstrating a congenital weakness of the internal sphincter and its supports. When these women were asked to cough, the downward pull on the "funneled" sphincter permitted a jet of urine to escape.

These cases once more demonstrate the fact that a perfectly well supported bladder base does not guarantee urinary continence in the erect posture if the support of the internal sphincter is incompetent.

It is well known that women may develop stress incontinence for the first time after a hysterectomy or after a cystocele repair. This embarrassing situation has been difficult to explain. One such case came to study.

Mrs. F. H., BIH No. 31005A, a 53 year old nullipara, had a hysterectomy elsewhere in 1940. Following this operation she developed severe stress incontinence. The physical and pelvic examinations were not remarkable. The fluoroscopic study of her bladder (Fig. 9) revealed the typical lesion of stress incontinence.

Just how a hysterectomy in some cases will interfere with the support of the internal sphincter is not clear at present. Further investigation of this problem is planned.

SUMMARY

The mechanism of urinary control in the normal female consists of two parts: the internal sphincter and the pubococcygeus portion of the levator ani. The latter is particularly important for urinary control in the erect posture.

Exertional incontinence results from failure of the pubococcygeus to support the bladder neck.

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ANTERIOR POLIOMYELITIS; EARLY AND LATE ELECTRICAL STIMULATION OF THE MUSCLES

STAFFORD L. OSBORNE, Ph.D., A. J. KOSMAN, Ph.D., H. D. BOUMAN, M.D., ROBERT T. McELVENNY, M.D., and A. C. IVY, Ph.D., M D., Chicago, Illinois

SACHS in 1910 wrote that the aim of therapy for the patient with anterior poliomyelitis should be to exercise muscles which cannot be exercised voluntarily. For this, he recommended the use of a form of electrical current which would yield the best contraction with a current of moderate strength. Williams and Levick concurred and maintained that the treatment should be applied early after the diagnosis of the disease.

From 1939 to 1946, a series of articles appeared (5-14, 16-21, 25, 28) which present evidence clearly establishing that the appropriate electrical stimulation of denervated muscle in laboratory animals retards the loss of weight and strength. However, few observations have been made on man. Doupe, Barnes, and Kerr obtained no effect in man when the rate of recovery of muscles after suture of the radial nerve was followed with and without galvanism. In the light of present knowledge the treatment used was inadequate and the criterion used was inappropriate. Shirley Jackson, in 1945, intensively treated patients with ulnar paralysis and obtained favorable results. Liu and Lewey reported that they obtained results similar to those of Jackson, though in their cases the muscle atrophy was far advanced (6 to 20 months) when treatment was started and they treated their patients for only a relatively short period.

In 1940 an investigation was started to ascertain the therapeutic value of electrical stimulation of denervated muscle. It was felt that no previous investigator, except Fischer had used an optimal stimulus on the basis of what was known regarding the electrical excitability of muscle. In the first phase of this investigation, a systematic search was made to find the wave form frequency and intensity of the current most suitable for stimulating and retarding atrophy of denervated skeletal muscle. The second phase involved a controlled study on animals to ascertain the various factors other than the nature of the current which might retard the rate of loss of weight and strength of denervated muscle. The present article represents the application of our observations on animals to patients with anterior poliomyelitis. The results on patients with a muscle denervated by section of a nerve will be reported later.

Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

From the Departments of Physical Medicine, Physiology, and Orthopedic Surgery, Northwestern University Medical School.

Dr. Bouman is now at the Department of Physical Medicine, University of Wisconsin.

Dr. Ivy is now at the University of Illinois College of Medicine, Department of Clinical Science.

METHODS

Late group. Because patients were not available in the early stage of the disease when the experiment was started, it was necessary to select patients who had had anterior poliomyelitis for some time. However, this was an advantage because it enabled us to work out the technique to be used in stimulating the paralyzed or paretic muscles. It was important to have our technique mastered before undertaking treatment in the early stage. Thirteen late patients were selected for treatment. These patients had had the disease for periods ranging from 6 months to 6 years.

Early group. Later, when the epidemic of 1946 occurred in Chicago, it was possible to select 7 patients as soon as they entered the Chicago Municipal Contagious Hospital, and the diagnosis of anterior poliomyelitis was made. The same number of patients were selected as a control group. The selection of both groups was made on the basis of the muscles involved and the apparent extent of the paralysis. At this stage of the disease, it is obvious that such a selection is very arti-

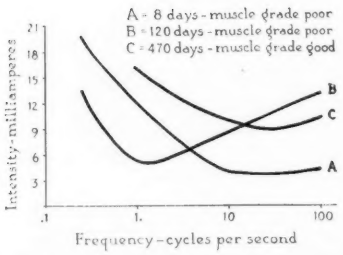

Fig. 1. Intensity-frequency curves of right hamstrings, patient 17, showing the change in the shape of the curve from the 8th to the 417th day after onset, during which considerable recovery had occurred. The initial and final curves are essentially normal.

ficial and open to much criticism. When 2 patients had the same muscle, or group of muscles involved, the patients whose muscles showed the lower grade in the muscle strength test was selected for treatment while the favored muscles of the other patient were selected as a control.

Testing procedures. As soon as the diagnosis of anterior poliomyelitis was made, and prior to treatment, the paralyzed or paretic muscles were given a manual strength test. The method used was that advocated by the National Foundation for Infantile Paralysis. The same physiotherapist always made successive examinations on the same patient.

In addition, the muscles were tested for the reaction of degeneration. This test proved unsatisfactory, especially for children. The tests were difficult to duplicate, even though made by the same examiner.

Electromyograms were recorded with a two-channel type A Offner electroencephalograph equipped with ink writer. The patient was enclosed in a shielded room during the entire examination. The electrodes were of copper, measuring 2.5 centimeters by 5 centimeters. They were coated with Cambridge electrode jelly, and two of them were securely attached by means of "Scotch" tape to the skin over each muscle being examined. In each instance the affected muscle, its antagonist, and the identical contralateral pair were examined. The examination was made as follows: (1) an active movement of one muscle, recording from the active muscle and its antagonist; (2) repeating (1), but recording from the contralateral pair; (3) active movement of antagonist and recording from active muscle and antagonist; (4) repeating (3) but with recording from identical pair; (5) this entire procedure was then repeated with the contralateral pair. A similar procedure, but with passive motion, was carried out. The range and duration of the passive movement was kept constant as possible for each muscle. In some instances the active movement was carried out against resistance.

Intensity-frequency curves of the muscles selected for treatment were taken. A sine wave current was used in this test because the muscle response would always occur at the same point (peak) of the cycle. Frequency was plotted against current intensity (Fig. 1). The current intensity sufficient to produce a threshold contraction was recorded. This curve enabled us to select the frequency to be used for treatment.

Circumferential measurements were taken from a constant distance from a set anatomical landmark. Contralateral parts were used as a control for the late group.

All the tests were repeated every 3 months until discharge. In addition, a subjective evaluation of the patient's progress was made.

Treatment. Once a patient was selected for electrical muscle stimulation, the muscles were stimulated daily for 6 days a week. The generator used was a "Variable Frequency Wave Generator" built to yield a current form and range of frequencies which have been found (26) to be essential. With this generator it is possible to develop the maximum tension in the muscle with the minimum current intensity. The current delivered by it is sinusoidal in form (Fig. 2a). The frequency of the current can be varied from two to six thousand cycles per minute. It is possible to change gradually from one frequency to another while the patient is in the circuit. With frequencies from thirty to six thousand cycles per minute we find it more convenient to convert cycles per minute to cycles per second. Thus, it is less cumbersome to speak of one-half to one hundred cycles per second. When the current reaches a frequency of two to one hundred cycles per second, the current may be modulated or surged 100 per cent sinusoidally to

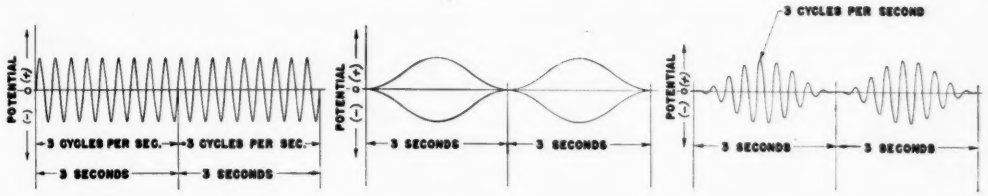

Fig. 2. a, Fundamental sinusoidal current 3 cycles per second. b, Modulating envelope of 3 seconds' duration or 20 modulations per minute. c, Modulated sinusoidal current with carrier frequency of 3 per second.

prevent a continuous tetanic contraction of the paretic muscle without relaxation (Fig. 2b). Modulation of the fundamental sine curve (Fig. 2c) prevents this and gives a graduated contraction similar to normal activity. The number of modulations per minute (Fig. 2b) determines the contraction rate of the muscles stimulated. This current we have termed a "modulated sinusoidal current" with a carrier frequency of two to one hundred cycles per second (Fig. 2c).

The frequency to be used for treatment was selected from the intensity-frequency curve similar to that illustrated in Figure 1. The frequency requiring the lowest current intensity for a threshold contraction was selected. This initial frequency was used until later examinations showed the muscle responded maximally to a different frequency. When the frequency was two or more cycles per second this fundamental wave was modulated as previously explained. The modulation rate (the rate at which the muscles contracted and relaxed) was maintained consistently at a rate of twenty-four times per minute throughout the entire course of treatment.

The complete technique of applying the electrodes to the muscles under stimulation will be dealt with in another communication. In some instances the unipolar technique was used while in others it was necessary to use a bipolar application. Patients differed a great deal, and one could never predict with precision just where the point of maximum muscle irritability would be found. When possible, the muscle was made to contract against resistance, either by working against a weight, or tying a foot, for instance, to the leg of the treatment table. Vigorous muscle contractions were secured. Each muscle, or group of muscles, was stimulated daily. The muscles were stimulated for 10 minutes unless fatigue occurred. Contrary to clinical teaching there is no danger of stimulating to, or beyond, fatigue, but it has been shown (20, 21.) that it is a waste of time because, unless tension is developed in the muscle, treatment is useless. Stimulating a muscle four times with appropriate rest periods between stimulations has been found (21) to produce maximum results. However, we stimulated the muscles only once daily.

The lower extremities of our patients appeared to have subnormal temperature; therefore, we found that a preliminary application of heat was desirable. We used a heat cradle of incandescent light bulbs for this purpose.

Since this study was concerned with human patients, physiotherapy other than electrical stimulation was used. In the "late group," the physiotherapy they had received previously was continued. In the "early group," treatment consisting of heat, passive stretching, and muscle re-education exercise was given three times weekly. Crutch walking was instituted as early as possible.

RESULTS IN THE LATE GROUP

The 13 patients in the group ranged in age from 2 years to 35 years. Four were females. The electrical stimulation was started from 6 months to 6 years after the acute onset of the disease; for example, 1 patient 6 years after; 2 at 2 years; 1 at 1 year; 1 at 9 months; 2 at 7 months; and 4 at 6 months; the usual muscles were involved and need not be listed here.

In these 13 patients, a total of 48 muscles were treated for from 4 to 18 months, the average being 9 months, and a total of 36 muscles were not treated.

The current used for stimulation, or the range of electrical excitability of the muscles stimulated. Eighteen of the muscles responded maximally to an unmodulated sinusoidal current ranging in frequency from 15 to 60 cycles per minute. Thirty of the muscles responded maximally to a modulated sinusoidal current with a carrier frequency varying from 5 to 15 cycles per second. The largest number, 50 per cent, responded to a modulated sinusoidal current with a carrier frequency of 5 cycles per second. Another 35 per cent showed a maximal contraction when stimulated at a frequency of 1 per second or less. Since the optimal frequency to produce a maximal contraction in normally innervated human muscles ranges from 15 to 100 cycles per second, all but 4 of the muscles stimulated by us may be considered to be partially denervated. The more fibers denervated in a muscle the lower the frequency required to give a maximal contraction at minimal intensity.

Of the 48 muscles stimulated, 30 showed no change in the frequency required to yield a maximal contraction during the course of treatment; in 2 the frequency decreased showing some further degeneration; and in 16 the frequency increased indicating either a recovery in some of the motor neurones or a hypertrophy of the normally innervated muscle fibers.

Measurement of girth. In 10 of the 13 patients it was possible to make reliable measurements of girth of either the leg, thigh, or arm. The girth measurement constituted an attempt to quantitate what was detected with the eye in some cases, or recorded with the camera. Whether the difference in the means between the initial and final average could be due to chance experimental error in making the measurements, was determined by statistical methods.

Every "final" measurement made was greater than the initial measurement. The average of the initial measurement of 18 lower legs treated was 21.8 centimeters and the measurements at the end of the treatment was 23.2 centimeters. This difference of 1.4 centimeters is significant ($t = 5.38$). The average initial measurement on the 14 thighs treated was 30.8 centimeters and the "final" measurement was 32.7 centimeters. The difference of 1.9 centimeters is significant ($t = 4.75$). The average initial measurement on the 13 arms measured was 19.2 centimeters and the "final" was 21.5 centimeters. The difference of 2.3 centimeters is significant ($t = 8.8$).

The increase in girth was not due to an increase in subcutaneous fat. Nevertheless, because 6 of the 10 patients were in various stages of growth (2 to 16 years of age), the possibility that growth was responsible had to be considered. Of the 6 patients, it is notable that 5 of them showed a greater increase in the girth of the treated extremity. The increase varied from 0.32 to 1.91 centimeters, the first figure being almost negligible but consistently observed. These patients had been afflicted, 1 at 6 months, 2 at 7 months, 1 at 10 months, and 1 at 12 months prior to the start of electrical stimulation. Improvement then was observed although they had had complete motor paralysis for 6 months or longer.

The other 4 patients, 19 years or over deserve some special reference. *Patient 8*, a female aged 20, was afflicted in 1940, 6 years prior to reporting for this experimental study. This patient had received the best physiotherapeutic treatment available. Except for the right gastrocnemius which yielded a "trace," the muscles of both legs were completely paralyzed as regards voluntary contraction. Under treatment the girth of both thighs and both legs increased (stimulation 8 to 10 months). *Patient 11*, a male aged 35, who was afflicted 21 months previously, had the triceps of one arm treated for 13 months and the girth increased 3.49 centimeters. *Patient 13*, female aged 27, was treated for paralysis of both legs which had been present for 6 months. The girth increases ranged from 2.86 to 4.76 centimeters. *Patient 12*, a male aged 19, received treatment of the thigh and lower leg; also 6 months after the onset of the disease; no increase in girth occurred but an improvement in strength was measured.

Measurement of strength. The results obtained on the measurement of strength are shown in Table I. It is to be noted that 36 muscles were untreated and 48 were treated.

In selecting the muscles for treatment we decided to handicap the treatment by select-

ing a large number with "zero" strength for treatment and selecting a large number with "fair" strength for no treatment. This was inadvisable from a statistical viewpoint, which teaches that the controls and treated muscles should have been equally distributed between the various grades of strength. Though greater improvement occurred in the muscles electrically stimulated, the difference and improvement is not statistically significant. Nevertheless, the increase in strength is in the same direction as the increase in girth. When the increase in strength is correlated with the increase in girth a good degree of correlation is obtained (the correlation coefficient was $r = +0.69$).

General observations. Twelve of the thirteen patients manifested objective improvement relative to girth, strength, or both, during the period of treatment of one or more of their paralyzed muscles as compared to nonstimulated muscles. Improvement, however, also occurred in nonstimulated muscles.

Four of the 13 patients, whose muscles had been paralyzed for 7, 9, 10, and 25 months, showed no improvement in voluntary motor function during the 12 to 18 months of observation according to the subjective judgment we formed by visually studying them. One patient showed neither objective nor subjective improvement after 5 months of treatment and was referred for operation to stabilize the ankle to counteract foot drop. The remaining 8 did manifest improvement in voluntary motor function, and their stimulated muscles had been paralyzed in 3 for 6 months, in 1 for 7 months, in 1 for 11 months, in 2 for 12 months, in 1 for 21 months, and in 1 for 6 years.

The following protocols indicate the type of "subjective" improvement observed by us.

Patient 2. Male, 31 years of age; electrical stimulation started 2 years after onset. At the initial examination the left knee joint was unstable and tired easily. After 5 months of treatment the knee joint was more stable and less easily fatigued.

Patient 4. Male, 4 years of age; electrical stimulation started 7 months after onset. At initial examination the left arm could not be abducted to side or front and elbow flexion was weak. After 1 year of treatment the arm was abducted side and front 10 times each, raised overhead 8 times without load, and abducted 3 times with a 1 pound load. Forearm flexion definitely improved.

TABLE I.—STRENGTH CHANGES IN 36 UNTREATED AND 48 TREATED MUSCLES IN THE "LATE GROUP" AND 59 TREATED MUSCLES IN THE EARLY GROUP; THE PATIENTS FOLLOWED FROM 12 TO 18 MONTHS.

Grade	No. of muscles in initial grade	Grade at end of experiments						Points of improvement
		Zero 0	Trace 1	Poor 2	Fair 3	Good 4	Normal 5	
A. 36 treated muscles, "late group"								
0	1	1						0
1	9		6	3				3
2	3			2	1			1
3	23				12	11		11
4	0							—
Total	36	1	6	5	13	11		15*
B. 48 treated muscles, "late group"								
0	21	11	9	1				11
1	16	1	9	3	2	1		9
2	4		2	0	1	1		1
3	7			1	2	4		3
4	0							
Total	48	12	20	5	5	6		24†
C. 59 treated muscles, "early group"								
0	18	9	9					9
1	28	4	11	4	4	5		23
2	9	1	1	1	6			3
3	4				1	2	1	4
4	0							
Total	59	14	21	5	11	7	1	39‡

* 15/36=41% improvement as a group.
† 24/48=57% improvement as a group.
‡ 39/59=66% improvement as a group.

Patient 6. Female, 3 years of age; electrical stimulation started 12 months after onset. At initial examination the patient could not sit up; could not balance with crutches and braces; could not crawl without brace; and wore two long leg braces and crutches. After 10 months of treatment, patient sits up well with good posture, wears one leg brace and crutches, is less easily fatigued; but balance is unimproved, and knocks knees.

Patient 8. Female, 20 years of age; electrical stimulation started 6 years after onset. At initial examination patient wore 2 long braces and crutches, could walk 25 feet twice daily with marked fatigue, balanced alone with braces for 1 to 2 seconds, with 2 braces was able to get out of wheelchair alone. After 9 months of treatment, patient uses 1 long leg brace and 2 crutches, walks 300 feet twice daily with same fatigue as for 25 feet previously, balances

a

b

Fig. 3. The amount of atrophy 15 months after onset of the disease. a, Patient 18; b, patient 19. Both patients have flail lower extremities. Patient 18 showed no decrease in girth of thigh or leg during 14 months and lost 8 pounds of body weight.

alone with braces for 20 minutes, and with one brace can get in and out of wheelchair alone.

Patient 10. Male, aged 2 years; electrical stimulation was started 6 months after onset. At the initial examination one leg brace was worn, activity was limited, and child crawled and preferred to go without brace. One year later, one leg brace was worn and activities of a normal three year old child were performed, such as climbing and walking; cannot run and ride bicycle or scooter.

Patient 11. Male, 35 years of age, who had been afflicted 21 months prior to the application of electrical stimulation. On first examination he was using 2 drop foot braces and 2 crutches and was exhausted after walking 50 feet with apparatus and aid and had to rest for one hour before he could repeat. He was able to balance and stand alone with support for 1 or 2 minutes but could not go up or down stairs with or without aid and bend and touch the floor and straighten up again. He could extend the forearm against gravity with great effort. *After 10 months of treatment* he could walk 125 feet with braces and crutch and could repeat every 5 minutes. He could ascend one flight of stairs by holding railing and bend over, touch floor, and straighten up. He was also able to extend forearm against a 1 pound weight five times. After 13 months he discarded the right ankle brace, drives his car, can sit on chair without support.

Patient 12. Male, aged 19 years; electrical stimulation started 6 months after acute onset of disease. At the first examination he dragged right foot and was exhausted after walking 200 feet with crutches. He could ascend stairs with great effort but could not do a deep knee bend or bend to touch toes and return. He could not dance or play drums. After 11 months of treatment he walked any distance desired, climbed stairs one at a time with ease, used streetcars, dances and plays drums professionally, drives a car and does not drag the right foot. Six months later he rode a bicycle and played a base drum with right foot for an entire evening.

Patient 13. Female, 27 years of age; electrical stimulation started 6 months after acute onset of disease. At the initial examination the patient after taking five steps with two crutches developed tremors in both arms and was able to stand with two crutches for 10 to 20 minutes. She was unable to get into or out of wheelchair and to dress herself. After 9 months of treatment the patient could walk 50 feet on crutches and 200 feet in walker. She could dress herself and get into and out of wheelchair or bed unaided, and use left leg working foot pedal of sewing machine.

All these 8 patients, though the muscles stimulated had been completely paralyzed for 6 months to 6 years, showed real functional improvement during the period of treatment, the least improvement being shown in the case of patient 8.

RESULTS IN THE EARLY GROUP

During the 1946 epidemic a group of 7 patients were selected for treatment during the acute course (first 10 days) of the disease on the basis of the severity and extensiveness of the paralysis as determined by strength tests, electromyography, and clinical experience. A "control group" of less afflicted patients was selected for observation. Both groups received the usual physiotherapeutic treatments. Electrical stimulation was started from 10 to 34 days after the acute onset of the disease and continued from 11 to 14 months.

Electrical excitability of muscles stimulated. The frequency required to yield a maximal contraction was followed. At the start of treatment, of the 57 muscles stimulated 5 responded maximally to a frequency of 15 cycles per second; 15 to a frequency of 10 cycles per second; 22 to 5 cycles per second; 1 to 3 cycles per second; and 14 to 1 cycle per second. At the end of the treatment period, 5 responded maximally to a frequency of 15; 11 to 10; 33 to 5; 3 to 3; and 5 to 1 cycle per second.

Judging from the changes in the frequency required to produce a maximal contraction, 21 remained the same, 21 improved, and 15 became worse.

Measurements of girth. Of the 7 patients, only 2 showed any decrease in the girth of the paralyzed extremities; 1 of these patients lost 31 pounds during the period of therapy and the other 8 pounds.

When the girth measurements of the lower leg are averaged the initial was 28.2 centimeters and the final 29.3 centimeters ($t=2.68$); those of the thigh were initially 39.1 centimeters and finally 40.1 centimeters ($t=1.33$); those for the upper extremity initially 24.9 centimeters and finally 25.8 centimeters ($t=1.88$). Though these differences were not significant it is quite notable that the paralyzed extremities did not lose any girth but tended to gain. *In view of the fact that in the one year of therapeutic observation there was no significant change in body weight, except in the 2 cases mentioned, it is clear that the stimulation or treatment very definitely prevented atrophy.*

This prevention of atrophy is illustrated in the two photographs of flail legs shown in Figure 3.

Measurement of strength. Fifty-nine muscles were stimulated. Of these, 31 improved in strength, 22 remained the same, and 6 became weaker (Table I).

As the strength tests were repeated, it was quite evident at the second test that 10 to 14 days after the acute onset of the disease was too early to grade the full extent of the paralysis; according to our observations, 1 month after the acute onset of the disease would be an approximate period for such appraisal.

Since the muscles selected for treatment in the "late" and "early" groups were comparable in regard to the initial muscle grades of strength, it is notable that the "final" grades are also comparable. This fact suggests that time is gained by starting treatment early.

General observations. All 7 patients regardless of the initial severity showed definite to marked improvement as would be expected. It is believed that the presentation of a protocol showing the improvement of each patient is unnecessary.

THE RESULTS OF ELECTROMYOGRAMS AND RESPONSE TO STRETCH

Electromyograms were made on all the "early" patients and on all of the "late" patients who showed definite evidences of abnormality. Such evidences of abnormal innervation as prolonged stretch-reflex "spasticity," and as activity on the heterolateral side on either active or passive movement were followed.

As has been reported by others, evidence of "spasticity," and abnormal reflex innervation was found in all the early cases. In our early cases it had disappeared or had markedly decreased at varying time intervals up to 7 months. In 1 of the patients who had not received electrical stimulation, spasticity on stretch and heterolateral activity still persisted, being increased over the early recordings, at 15 months.

Three of the patients in the "late group" showed a disturbance of reflex innervation. Patient 8 was particularly interesting because of the interval of 6 years between the acute attack of the disease and the start of electrical stimulation. In this case the prolonged stretch reflex or "spasticity" and heterolateral activity disappeared during the period of treatment (10 months). Patient 11 who had been afflicted 21 months prior to the beginning of electrical stimulation manifested a very definite spasm in response to stretch as well as heterolateral activity; this had almost completely disappeared after 2 months (Fig. 4). In patient 12, whose right leg had been paralyzed for only 6 months the evidence of abnormal reflex innervation disappeared after 12 months of therapy.

These observations are not recorded with the idea that electrical stimulation was specifically responsible, but to indicate how long evidence of abnormal reflex innervation may persist.

DISCUSSION

The observations made during this investigation have proved several points but leave the most practical points open for further investigation.

When this work was first contemplated we were told that one could not cause the atrophied muscles of the "late" cases of anterior poliomyelitis to contract by means of electrical stimulation, and particularly the paralyzed muscle of the "early" case, without causing intolerable pain. We have definitely demonstrated this view to be false. Such a view was based on a failure to comprehend the full significance of the physiological principle of the intensity-frequency curve in electrical stimulation.

Our results on the early cases show that atrophy of the muscles can be markedly retarded, even prevented for one year, by adequate daily electrical stimulation of the muscle of the completely paralyzed or so called "flail" limb. Our measurements of girth also show that some hypertrophy was obtained in the paralyzed muscles of the "late" cases. This was slight on the average but nevertheless was an increase that could have occurred by chance or error in measurement in less than 1 out of 100 cases. We had anticipated these results because of our work and that of others on lower animals and because of our unpublished observations on human patients with peripheral nerve paralysis. Since it is clear that the atrophy of denervated muscle is not

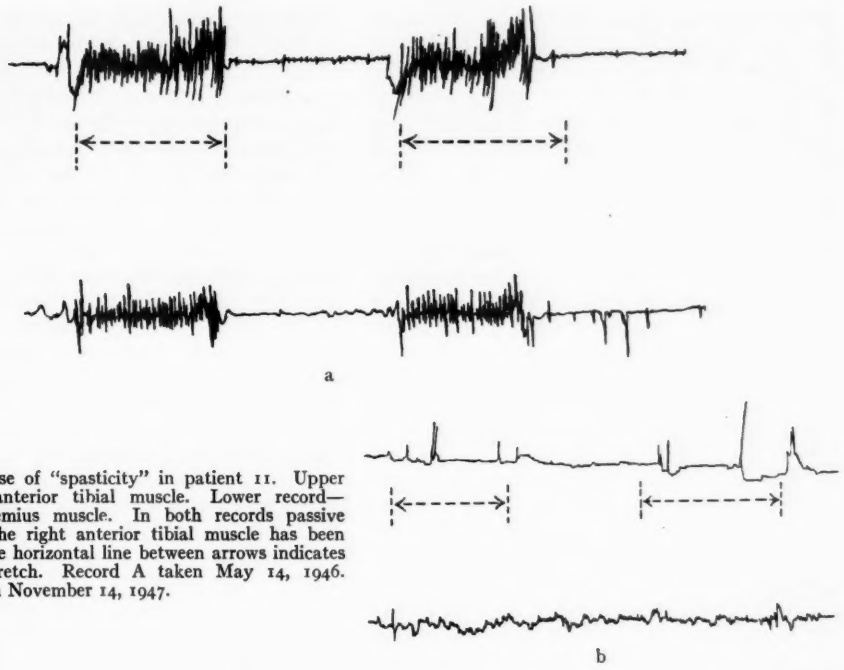

Fig. 4. Course of "spasticity" in patient 11. Upper record—right anterior tibial muscle. Lower record—right gastrocnemius muscle. In both records passive stretching of the right anterior tibial muscle has been performed. The horizontal line between arrows indicates duration of stretch. Record A taken May 14, 1946. Record B taken November 14, 1947.

due to overwork or constant fibrillation (29, 30) and that muscles atrophy from disuse, and since Bowden and Gutman (1) have found that few if any muscle fibers in man have undergone complete degeneration to fibrous tissue in 3 years, it is reasonable to believe that appropriate electrical stimulation will cause such muscle to contract and may cause some hypertrophy. It has been shown that denervated muscle can be caused to contract in a "normal" manner by the appropriate electrical stimulus and that the earlier the application of treatment (10, 11), and with the application of some load (5, 6, 16-21, 25), the more the atrophy and loss of strength is retarded. There is no reason why these facts should not apply to those fibers in a muscle which are degenerating slowly as a result of the destruction of the anterior horn cell that supplies them as well as to those which are atrophying due to disuse or absence of voluntary use. The negative results reported in the literature were obtained with inappropriate currents; this also applies to the excellent investigation of Chor and his associates which was done specifically to ascertain the value of currents used by clinicians at the time that work was done. The negative results were due to a failure to apply the physiological principle of the intensity-frequency curve to the selection of the most appropriate electrical stimulus for a maximal or effective contraction.

To retard atrophy the treatment must be adequate. This means that (a) vigorous contractions with tension must be secured, (b) the proper wave form of current is important, (c) the treatment must be given daily and each muscle stimulated two or three times, (d) and the muscle should be stimulated to the point of fatigue. To stimulate a fatigued muscle with the proper current is not injurious to the muscle; it is simply a waste of time since the muscle does not develop tension. As already stated it is agreed that to prevent atrophy a vigorous contraction with tension is required. To obtain a vigorous contraction with tension in an unanesthetized patient, a current of low intensity must be used, because the patient

will not tolerate the pain. To obtain a maximal contraction without pain or the least pain, a current of optimal frequency and minimal intensity for the particular muscle must be found. The wave form is also important. For example a vigorous contraction cannot be obtained in a patient with an interrupted direct current because the patient will not tolerate the required current intensity (20). This is especially important in case of anterior poliomyelitis where sensory innervation is intact.

Although the data on the changes in strength of the paralyzed muscles in relation to electrical stimulation are not statistically significant, the average improvement of the 48 treated muscles in the "late" group was greater (57 per cent) than in the 36 untreated muscles (41 per cent) (Table I, A and B). The use of some more accurate and yet simple test for muscle strength would have made these data more satisfactory. Even with the tests used, our hindsight indicates that the number of treated and untreated muscles in each grade should have been approximately equal. Our desire to handicap the electrical therapy by choosing a large number of muscles with zero grade strength and our sympathy for the patient subdued our scientific judgment. In an experiment of this sort, it is unwise to use an experimental design that handicaps the procedure being evaluated. Our experience with the "early" cases demonstrates the impracticability of trying to use a control and treated group of patients. The variation is so marked between patients, even in the same epidemic, that at least 50 control and 50 untreated patients would be required. Even then, 1 month should elapse between the onset of the disease and the pairing off of patients into a control and treated group. In addition, a large staff would be required to give the treatment and make the measurements. Our experience teaches that it is much better, as was done in the "late" cases, to choose patients so that they may serve as their own controls. This eliminates also such variables as sex, weight, age, homologous parts, growth, and the psychological factor that one group is being treated differently from the other.

Even when the same patient is used for his own control, the factor of the effect of a new treatment and its daily application on the will and effort of the patient to improve cannot be controlled. Any properly motivated therapy given daily tends to "push" these patients to do better. The effect of "push" therapy, however, should in some instances affect the untreated as well as the treated muscles. It is difficult, for example, to determine exactly whether the improvement in the untreated muscles in the late cases (Table I, A) was due to "push" therapy or to other factors. The fact that a change occurred in the frequency-intensity curve does not answer this question. In fact, we can conceive of no perfectly designed experiment to establish categorically the effectiveness of a therapy such as electrical stimulation, or similar therapeutic measures in poliomyelitis.

Adequate electrical stimulation has a remarkable psychologic effect on the patient for several weeks or longer. It is a great relief to a patient to see and feel movement in a limb or muscle which they have not been able to move for 2 weeks up to 6 years. We have gained the impression that this psychic stimulation plus the kinesthetic sensations of muscle movements of a set of muscles facilitates the re-educational process. Gutmann and Guttmann (10) advise that electrical exercise be continued in peripheral nerve patients until motor recovery is satisfactory because it seems to augment active exercise where the patient cooperates poorly when innervation is taking place. Jackson also believes that electrical exercise aids the voluntary action of muscle when given at the time of reinnervation. This is a claim that could be checked in animals and perhaps patients through the mechanism of a conditioned reflex.

Theoretically the retardation of atrophy and loss of strength in a muscle or group of muscles until a reversible change in the anterior horn cell has occurred should serve not only to encourage the patient but to facilitate re-education and substitution or psychomotor activities directed to the previously completely paralyzed part. It would appear that electrical stimulation combined with exercise therapy should provide the best possible treatment for this disease where surgery is not definitely indicated. Such ideas cannot be

proved by any quantitative data submitted by us but are supported by our experience in observing the improvement which occurred in the "late" cases we treated. In such patients it must be remembered as is true of all rehabilitative efforts, that a small gain in ability to care for oneself is of great practical value though not so evident to the observer.

SUMMARY

1. A new type of generator was used in this study. The generator supplied a pure sinusoidal current which could be varied at will from two to six thousand cycles per minute.

2. The maximum contraction and tension can be secured in paralyzed muscle with a minimum current intensity when consideration is given to both current form and current frequency.

3. Children from 2 to 16 years of age and afflicted with anterior poliomyelitis were given vigorous muscle contractions, and tolerated the current well.

4. Electrical stimulation of the muscles was given to 7 patients as soon as the diagnosis of anterior poliomyelitis was made (the "early" group). Thus treatment can be instituted during the acute phase of the disease without injury to the muscles or the patients. It was also given to 13 patients who had the sequelae of the disease for from 6 months to 6 years (the "late" group).

5. In both groups of patients the bulk of the muscles stimulated daily was favorably affected. There was a statistically significant increase in size of the treated muscles for the "late group." In the "early group" where the initial limb measurements were taken before much atrophy had occurred, the mass of the treated muscles was definitely maintained.

6. There was some improvement, though not statistically significant, in the strength of the muscles stimulated.

7. Electromyographic evidence in the "late" cases suggests that electrical stimulation may be of value in helping to restore normal innervation patterns of the involved muscles.

8. There was some evidence, though less tangible, that stimulation of the muscles was a distinct aid in helping the patient to gain a sense of muscle action needed, and that this was an aid in the re-education of the muscle when active exercise was attempted.

9. Treatment should start, according to our results, as soon as the diagnosis of anterior poliomyelitis is assured. However, in selecting muscle for purposes of studying a treatment, 1 or 2 months should elapse after the onset of the disease.

10. The rationale for the use of electrical currents in the stimulation of muscle is discussed.

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CONSEQUENCES OF SECTION OF THE PANCREATIC DUCT

An Experimental Study

H. L. POPPER, M.D., Chicago, Illinois

IN radical operations for primary carcinoma of the pancreas or duodenum, or for secondary involvement of the pancreas by carcinoma of the stomach or colon, transsection of pancreatic ducts has to be performed often. Also, unplanned and unintentional section of pancreatic ducts may occur and occasionally may not be recognized. What are the consequences of such an injury to the pancreatic duct?

In the textbooks on surgery, little space is devoted to surgical injuries to the pancreas, which are usually subject to general discussion only, without details. As far as experimental work is concerned, only two references were found in the recent literature regarding experimental transsection of the pancreas without ligation of ducts.

In a study on dogs of the results of partial excision of the head of the pancreas with scalpel, cautery, and high frequency knife, Tripodi and Sherwin clamped and ligated bleeding vessels after the excision and sutured omentum over the raw end of the pancreas without ligating the pancreatic duct. Reoperation on the animals after an interval of several weeks did not reveal evidence of postoperative peritonitis, collection of pancreatic secretion or fat necrosis.

In his book on *Surgery of Pancreatic Tumors*, Brunschwig reports on partial pancreatectomies in 6 monkeys. In 2 monkeys, the head of the pancreas was removed by transsection of the neck with ligation of bleeding vessels, without isolation or ligature of transsected ducts, however. One animal died after 8 days with gastric dilatation, with some edema of the pancreas, but without fat necrosis. Another died within 24 hours with acute pancreatitis and acute fat necrosis. In the other 2 monkeys, the same procedure was followed, but the cut end of the pancreatic stump was ligated with silk. Neither animal showed any postoperative ill effects.

Considering the lack of systematic experimental observations, it seemed worthwhile studying in animals the immediate consequences of cutting the pancreatic duct and leaving it open.

Methods. The experiments were performed on 50 healthy mongrel dogs of both sexes, weighing from 7 to 12 kilograms. Under pentobarbital sodium anesthesia, the pancreas was exposed through a right rectus incision. In the first series, numbering 27 dogs, the main pancreatic duct was isolated, ligated close to the duodenum, and transsected. After probing the open pancreatic end of the duct for patency of its two main branches, the abdomen was closed without further manipulation. The dogs of this series are presented in four groups according to whether they were fed or starved before or after operation or were given special postoperative medication.

In the second series of 23 dogs, probes were inserted into the opened pancreatic duct and either one or both branches of the duct were incised along the probe for about 1 inch, which required transsection of a considerable portion of glandular tissue. In the starved dogs there was little bleeding from the pancreas. In the dogs that were fed preoperatively, the bleeding was more pronounced, but it was always easily controlled. After ligation of a few profusely bleeding vessels, the pancreas was compressed with hot sponges for a few minutes to stop the remaining small bleeders and the abdominal wall was closed. The dogs of this series are divided into three groups, representing those fed before or after operation or starved dogs respectively. No medication was given in this series.

Some of the animals of both series died a few days after operation. The others were

From the Department of Gastrointestinal Research, Medical Research Institute of Michael Reese Hospital, Chicago, Illinois.

Aided by a grant from the Rosetta Josephson Fund. The Department is in part supported by the Michael Reese Research Foundation.

sacrificed between the second and the twenty-fifth postoperative day. At autopsy, special attention was given to the presence of intraperitoneal fluid, of localized or generalized fat necrosis, to the condition of the pancreas, and to changes in the area of the cut pancreatic duct.

EXPERIMENTS AND RESULTS

Series 1: Pancreatic Duct Transsected between Pancreas and Duodenum

Group 1. Ten dogs, *starved before and after operation.* None of these dogs appeared to be sick after the immediate postoperative reaction was over. They were sacrificed between the third and the eighteenth postoperative day. Only 1 animal had a small amount of bloody fluid in the peritoneal cavity. One dog had a few pinhead sized fat necroses in the midline fat, and another had a few small fat necroses on the lateral surface of the mesoduodenum. Otherwise, there were no generalized or localized fat necroses in any of these dogs. The pancreas was somewhat indurated in 1 dog, markedly indurated in another, but appeared normal in the remaining 6 animals. The area of the cut duct was covered by granulation tissue in 1 dog, by a tag of omentum in 8 dogs, and by omentum as well as by duodenum in 1 dog. Thus the cut duct was sealed off in all the dogs. In animals sacrificed on the third postoperative day, the omentum could be separated from the pancreas by gentle traction. With a longer interval between operation and autopsy, adhesions between pancreas and omentum became proportionally firmer. In dogs sacrificed 18 days after operation, the omentum could be separated from the pancreas only by sharp dissection. After separating the omentum from the pancreas, the open pancreatic duct could be seen and probed in some dogs, but in others the opening of the duct was not visible. In 1 dog, a minute abscess had formed between pancreas and omentum. The duct system seemed slightly distended in 1 dog.

Group 2. Six dogs, *fed shortly before surgery*, but, with one exception, starved for 2 or 3 days afterward. While a number of these dogs seemed to be quite sick, others gave the impression of rather good recovery. The animals were sacrificed between the second and seventh postoperative day. Three of the dogs showed hemorrhagic intraperitoneal fluid. Four of the dogs, including the one fed postoperatively had large numbers of fat necroses scattered over the abdominal cavity and the retroperitoneal area; another dog had no generalized fat necroses, but a large area of fat necroses with edema was under the omentum which covered the region of the cut pancreatic duct. Three dogs had fat necroses in the pancreas; the dog fed before and after operation showed some induration of the pancreas; in the remaining 2 dogs, the pancreas seemed normal. In all dogs, except 1 with diffuse fat necrosis, omentum covered the pancreas and was loosely attached to the region of the pancreatic duct. However, in contrast to the starved dogs, numerous fat necroses and edema were found under this cover. Only 1 dog of this group showed rather minor changes, consisting of only a limited number of fat necroses between pancreas and duodenum.

Group 3. Six dogs, *starved before operation, but fed shortly afterward.* One animal died on the second day after operation. The other 5 were sacrificed: 2, on the second; and 3, on the sixth postoperative day. The autopsy findings were: bloody intraperitoneal fluid in 3 dogs; a moderate number of scattered intra-abdominal fat necroses in 3 dogs; large areas of localized fat necroses around the pancreas and fat necrosis and edema in the region of the cut duct in 4 dogs; and a moderate number of localized fat necroses in 1 dog. Only 1 dog had no fat necroses at all. In 3 dogs, the pancreas was moderately indurated, and 1 of them showed some dilatation of the pancreatic ducts. Otherwise, there were no changes of the pancreas. In all dogs, omentum covered the pancreas and the area of the cut duct, but fat necroses and some fluid could usually be found between omentum and pancreas.

Group 4. Five dogs, *starved before and after operation*, which were given subcutaneous injections of *pilocarpine** or of *prostigmine*† *postoperatively*. The dogs were sacrificed on the second or third postoperative day. The autopsy findings were: bloody intraperitoneal

*3 injections of 0.5 mgm. per kgm. at hourly intervals.
†3 injections of 1 mgm. at hourly intervals.

fluid in 1 dog; a moderate number of generalized fat necroses in another animal; localized fat necroses in the region of the pancreas and between the pancreas and the omentum in all 5 animals; and some fat necroses in the pancreas in 1 dog.

Series 2: Pancreatic Duct Slit Open

Group 1. Eleven dogs, *starved before and after operation.* In 4 dogs, one branch of the main pancreatic duct was slit open, and both branches in the remaining 7 dogs. Seven dogs were starved for 3 days after operation; 2, for 5 days; 1, for 7 days; and 1, for 8 days. A few dogs appeared quite sick for the first few days, but most of the animals showed remarkably little postoperative reaction. Two dogs died on the sixth day; and 2, on the seventh day after the operation. Three of these dogs died of pneumonia and 1 of diffuse fat necrosis with a large amount of hemorrhagic intraperitoneal fluid. The other 6 animals were sacrificed between the eighth and twenty-fifth postoperative day. All dogs except the 1 just mentioned showed only very few intra-abdominal changes. Only 4 had a small amount of bloody or pinkish exudate. One showed a few scattered fat necroses and 2 others showed a few fat necroses in the region of the pancreas. The area of the incised duct was covered in 1 dog by colon, and in the others by omentum. The firmness of the adhesion of omentum was in proportion to the time interval between operation and autopsy. The area of the incised duct was filled with a small clot in one dog and was slightly hemorrhagic in another. In 2 dogs, some purulent material was found between the incised duct and the cover of omentum. In 4 dogs the pancreas appeared normal, while it showed various degrees of induration in the remaining animals. There were no obvious differences between the findings in the dogs which had only one branch and those that had both branches of the main duct incised.

Group 2. Eight dogs, *fed a few hours before operation,* but *starved postoperatively* for 2 to 8 days. One branch of the pancreatic duct was opened in the first 4 dogs, and both branches in the remaining 4. Some animals were very sick postoperatively, and 3 died on the second, third, and fourth days, respectively. Another very sick dog was sacrificed the second day after operation. The other 4 dogs seemed to be in good condition and were sacrificed 8 and 9 days after operation. In 2 dogs, the appearance of well-being was in contrast to the autopsy findings, which revealed most extensive intra-abdominal changes. In summary, the findings in the 8 dogs of this group were: bloody or pinkish intraperitoneal fluid in 5, most extensive localized and generalized fat necrosis in 3, less extensive localized and generalized fat necrosis in 3, and no fat necrosis at all in 2 dogs. The area of the incised duct was covered by omentum in all but 1 of the dogs. In 2 there was suppuration under the cover of omentum. The omentum was firmly adherent only in the dogs without fat necrosis. The pancreas was partly hemorrhagic in 3 dogs, showed edema and fat necrosis in 1, and various degrees of induration in 3. Whether one or both branches of the pancreatic duct had been incised did not seem to affect the results.

Group 3. Four dogs, *starved preoperatively,* but given *food and* drinking *water with dextrose shortly after operation.* Both branches of the pancreatic duct were incised in the animals of this group. One dog died on the third, another on the fourth postoperative day. The other 2 dogs were sacrificed on the third and fifth postoperative day, respectively. All animals seemed sick in the postoperative period. The autopsy findings were: various amounts of intraperitoneal fluid in 3 dogs; extensive fat necrosis in 3; less extensive fat necrosis in the fourth. The area of the incised ducts was somewhat hemorrhagic in all 4 animals; it was covered by loosely attached omentum in 3 and by somewhat adherent omentum in the fourth. The pancreas was partly hemorrhagic in 1 dog, but it appeared normal in the other 3.

DISCUSSION

The experiments of series 1 demonstrated that transsecting the main pancreatic duct and leaving it open did not kill the animals within a short time and, under certain conditions, was not followed by intraperitoneal pathologic changes. The dogs that had been starved before and after the operation showed a minimum of intra-abdominal changes at the autopsy. The cut duct, with 1 exception, was

plugged by a small tag of the otherwise normal and freely movable omentum. This plugging was so efficient that there was no leakage of pancreatic juice even in the 1 dog in which the pancreatic duct was distended behind the plug. It was obvious that the plugging by omentum was a form of self-healing, and that spilling of pancreatic juice into the peritoneal cavity was impossible after the omentum had become densely adherent to the region of the transsected duct.

In contrast to these observations were the results in the other experiments of this series. With 1 exception, the dogs that had been fed before operation showed striking intraperitoneal changes at autopsy. The open duct was usually covered by omentum, but this cover had not succeeded in completely sealing off the pancreatic duct, and a large amount of fat necrosis and edema was frequently found under this cover as well as outside of it.

The dogs which had been starved before operation but given food shortly afterward, though most of them ate only part of the food, likewise showed marked changes. However, the fat necroses were mostly localized in the pancreatic region and were not so extensive as in the dogs fed before operation.

The fact that intra-abdominal fat necrosis was almost exclusively confined to the dogs which had been fed shortly before or after the operation suggested that increased postoperative flow of pancreatic juice, caused by the secretin liberating effect of preoperatively or postoperatively ingested food, played a decisive role. The observation that the intraperitoneal changes were much more extensive in the dogs fed before operation than in the ones fed afterward seemed to find its explanation in the fact that postoperative feeding could not be started before 8 to 10 hours after the operation, after the effects of anesthesia had worn off, and that the dogs took only part of the food thereafter.

To ascertain whether or not vagal stimulation of the pancreas has similar effects, experiments were performed in which the dogs were starved before and after operation, but were given vagotonic medication postoperatively. The dogs were sacrificed after only a short interval because we were interested mainly in the observation of the immediate intra-abdominal reaction. All the dogs had fat necroses in the pancreatic region and under the tag of omentum that covered the area of the transsected duct. This shows that vagal stimulation of pancreatic secretion also, though to a lesser degree than stimulation by secretin, interferes with the healing mechanism which is regularly found in starved animals.

Transsection of the main pancreatic duct without subsequent ligation was tolerated so well by the starved dogs and followed by so remarkably few intra-abdominal changes that we continued our experiments by studying the consequences of more extensive cutting of the pancreas. In the second series of experiments, pancreatic duct and glandular tissue were cut wide open, with results very similar to those in the first series of dogs.

The dogs starved before and after operation, with only 1 exception, showed merely insignificant intra-abdominal findings at autopsy, in spite of the extensive injury to the pancreas. The healing mechanism was the same as in the other experiments, only the omentum was adherent to a wider area, and the pancreas was more indurated.

Most of the animals that had been fed before operation showed extensive fat necrosis in the peritoneal cavity.

Though the postoperatively fed animals of this series took water freely—probably due to the more extensive surgical procedure—they refused food after the operation or vomited shortly after eating so that no feeding effect could be expected. Therefore, dextrose was added to the drinking water postoperatively and the dogs drank considerable amounts of it. Very extensive intraperitoneal changes were found in these dogs, similar to those in the dogs fed before operation.

It was evident in both series of experiments that in starved animals the peritoneum was protected from inflow of pancreatic juice by a most efficient sealing of the open pancreatic ducts. This was generally effected by omentum, though colon or duodenum were involved occasionally. However, the smooth healing in the staryed dogs cannot be explained by the plugging process alone. An arrest or at least a pronounced decrease of pancreatic secretion

must have occurred simultaneously with the plugging, because otherwise marked intraductal accumulation of pancreatic secretions would have resulted, with subsequent distention of the duct system; however, dilatation of the pancreatic ducts was found in only 1 dog.

Stimulation of the pancreas by liberation of secretin due to preoperative or postoperative feedings, and similarly by vagal stimulation, obviously counteracts the arrest of pancreatic secretion which occurred in the starved animals. Consequently, when the intraductal secretory pressure of the pancreas exceeds the adhesive power of the omental plug, leaking of pancreatic juice takes place and causes intraperitoneal fat necrosis. However, after a certain time, the gland no longer seems to respond to normal alimentary stimuli. This is similar to the findings in dogs with ligated pancreatic ducts and is confirmed by the results of serum amylase tests which showed an initial postoperative rise with return to normal after a few days, just as is the case after ligation of the duct. Autopsy revealed induration of the pancreas in a number of dogs of both series. This is the consequence of the sealing off of the pancreatic duct and, as is known from experimental ligation, is the forerunner of more or less complete atrophy of the glandular tissue, which eventually must take place if the pancreatic duct is occluded.

SUMMARY AND CONCLUSIONS

Transsecting the pancreatic duct or slitting it wide open, as a rule, does not cause intraperitoneal fat necrosis if the animal has been starved before and after operation. Following the operation, omentum attaches itself to the wound of the pancreas and plugs the open duct. At the same time, an arrest of pancreatic secretion seems to occur. After a few days, the omental plug is firmly adherent to the pancreas and the healing process is terminated as far as the prevention of leakage of pancreatic juice is concerned. However, the sealing off of the pancreatic duct, similar to closure of the duct by ligature, eventually is bound to lead to fibrosis and atrophy of the glandular tissue.

Preoperative or postoperative feeding of the animals is usually followed by extensive intra-abdominal fat necrosis, while postoperative vagotonic medication leads to similar but less extensive changes. Obviously, feeding is a more potent stimulus for pancreatic secretion than a few injections of pilocarpine or prostigmine. It is concluded that increased flow of pancreatic secretions, due to secretin as well as to vagal stimulation, offsets the protective plugging process. This allows pancreatic juice to enter the peritoneal cavity and to cause fat necrosis.

From these animal experiments, conclusions can be drawn which may be of importance in the treatment of surgical or accidental wounds of the pancreas and in surgery of the pancreas in general. The following measures are suggested for clinical trial:

1. If a pancreatic duct is transsected and if implantation into the intestinal tract is not feasible, it may be best to attach omentum to the ligated stump, since omentum seems to be capable of sealing off the duct even if the ligature should fail.

2. In the case of injuries to the glandular tissue of the pancreas, it may be advisable to attach omentum to the pancreas, even if the lesion of the pancreas has been sutured. This may help to reduce the incidence of postoperative pancreatic fistulas.

3. In cases of elective surgery on the pancreas, or when the gland may be injured in the surgical procedure, it seems advisable to prolong the routine period of preoperative starvation and to give preoperative medication which does not stimulate pancreatic secretion but which depresses it.

4. After operation on and injuries to the pancreas, it seems advisable to keep the external pancreatic secretion at a minimum for several days by inhibiting it through medication and by avoiding humoral as well as vagal stimulation of the pancreas.

Although these statements are based on controlled animal experiments, clinical observations will have to show to what extent they are applicable to clinical surgery.

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THE EXPECTANT TREATMENT OF PLACENTA PREVIA

A Study of 50 Maternal Deaths

CHARLES A. GORDON, M.D., F.A.C.S., and ALEXANDER H. ROSENTHAL, M.D., F.A.C.S.,
Brooklyn, New York

PLACENTA previa is an important cause of maternal mortality. Davis believes that at least half of the maternal deaths in the United States assigned to hemorrhage are due to placenta previa, and estimates that 15 to 20 per cent of all our maternal deaths are due to this cause.

In Brooklyn, where 1011 maternal deaths occurred in the ten year period 1937 to 1947, 145 were assigned officially to hemorrhage. Upon study of case reports of all maternal deaths, however, hemorrhage was found to be the chief cause of death in 290 cases. Placenta previa was associated with death in 50 cases.

Placenta previa is still a major complication of pregnancy though wider use of cesarean section and blood transfusion, particularly in the last decade, has considerably reduced its mortality. Recent definite trend toward complete abandonment of dilating bags and version with stricter limitation of operative procedures to cesarean section and simple rupture of the membranes should result in minimal mortality in communities where obstetrical resources are adequate.

It has long been believed and taught that there is no place for expectancy in the management of placenta previa, and that treatment should be initiated just as soon as the diagnosis has been made. The considerable fetal mortality has long been accepted as a natural corollary of early intervention. If there is little to support general belief that initial hemorrhage, even though it may not be serious, will be followed by others, any one of which may be fatal, expectant treatment should bring about substantial reduction in fetal mortality.

In 1945, Macafee (4) and Johnson, independently, yet almost at the same time, stated that initial hemorrhage is rarely or never catastrophic, apart from vaginal manipulation, and that recurrent hemorrhages do not lead to fatal hemorrhage. They feel certain that expectant treatment is safe and proper provided certain precautions are taken. Macafee has reported 191 cases with but 1 maternal death (0.5 per cent) and a total infant mortality of 42 (22 per cent). Johnson reported 79 cases with 1 maternal death and a fetal mortality of 22.2 per cent. It is of interest to find that Davis has reported from the Chicago Lying-In Hospital, where expectant treatment has not been practiced, 325 cases with but 2 maternal deaths (0.6 per cent) and a fetal mortality of 31.6 per cent. On the basis of these figures alone it would appear that the chief argument for expectant treatment is lowered fetal mortality.

Macafee (4) is willing to allow primigravidas, but not multiparas, to remain at home provided they live reasonably near the hospital and are "warned not to permit any vaginal examination before admission." He knows of no case in which a severe spontaneous hemorrhage occurred in a primigravida. Numerous small hemorrhages cause him no anxiety. Curiously enough, in only one of his cases was blood transfusion necessary.

Johnson will permit a patient with placenta previa to remain at home if hospitalization is impracticable for economic reasons, having her return to the hospital for blood study after bleeding episodes of any consequence. He would be surprised to learn of "a maternal death from placenta previa . . . where nature has been allowed to take its course as regards labor and delivery." In fact he offers a reward for such a case. He states that the placenta should be allowed to separate naturally and that "this is especially true if free bleeding is present."

Eastman believes that the recommendations of Macafee and Johnson "will do much good provided they do not result in callous-

TABLE I.—CAUSES OF DEATH

	Pelvic delivery	Cesarean section	Undelivered	Total
Infection	4	14	0	18
Hemorrhage	12	2	1	15
Rupture of uterus	8	0	0	8
Cardiac failure	0	2	0	2
Transfusion hemolysis	0	2	0	2
Pulmonary embolus	0	1	0	1
Postoperative shock	0	1	0	1
Eclampsia	1	0	1	2
Spinal anesthesia	0	0	1	1
Total	25	22	3	50

ness to hemorrhage." With this we agree, yet their importance warrants careful consideration. The expectant treatment advocated by both authors is based upon their experience and belief that hemorrhage, whether initial bleeding or subsequent and no matter how often repeated, will not cause death, in the absence of vaginal examination or manipulation.

Since we believe that the risk of this method of treatment may best be measured by careful review of the sequence of events which have preceded death in a considerable number of cases, we have studied 50 case reports of maternal deaths associated with placenta previa.

MATERIAL FOR STUDY

All 50 deaths occurred in Brooklyn in hospitals of various types. There were 10 primigravidas and 39 multigravidas; in 1 case parity is unknown; 58 were white women and 2 were negroes. The duration of pregnancy was 6 to 8 months in 13 cases, 8 months to term in 14 cases and 21 women were at term; in 2 cases the duration of pregnancy was not stated.

Cesarean section had been performed in 22 cases. Delivery from below had occurred in 25 cases; 3 women died undelivered. In 5 cases the first hemorrhage occurred after the onset of labor. The causes of death appear in Table I.

Placenta previa was complete in 25 cases, partial in 9 cases, and marginal in 12 cases; not stated in 4 cases

Hemorrhage followed several patterns with considerable variation in the time of onset, amount of initial hemorrhage, and the time and character of recurrent bleedings. It may be summarized as follows:

1. Initial profuse antepartum hemorrhage, 12 cases.
2. Spotting for 4 or 5 weeks followed by moderate or profuse hemorrhage, 3 cases.
3. Recurrent slight bleedings for 1 to 4 weeks followed by moderate or profuse hemorrhage, 15 cases.
4. Recurrent slight bleedings for 4 weeks to 4 months followed by moderate or profuse hemorrhage, 7 cases.
5. Initial moderate bleeding followed within 1 to 6 weeks by a second moderate or profuse hemorrhage, 7 cases.
6. One episode of bleeding in the 7th month, 1 case.
7. First hemorrhage intrapartum, 5 cases.

TABLE II.—CONDITION OF PATIENT BEFORE ACTIVE TREATMENT

Type	Good	Fair	Poor
2, Marginal	4	6	1
3, Partial	2	4	3*
4, Complete	6	10	9†
Unknown	–	3	2
Total	12	23	15

* Nephrosclerosis, 1 case
† Eclampsis, 1 case

It is not practicable to discuss the general condition of each patient before treatment was instituted or to describe hemorrhage in terms other than slight, moderate, profuse, and severe as in the case reports of death. As a result of hemorrhage, however, 13 women were in poor condition before active treatment; 7 were in shock, 5 actually in labor (Table II). In primigravidas antepartum hemorrhage was not severe in any case, except after rectal examination (2 cases). In 1 case in which severe hemorrhage occurred early in labor, brief clinical data are of interest:

CASE 1. In a patient of 25 years, severe hemorrhage occurred a few hours after the onset of labor in the 38th week of pregnancy. She was admitted to the hospital in shock, with a pulse rate of 140. Plasma and 500 cubic centimeters of glucose solution were administered, and cesarean section was performed. Hemorrhage continued postpartum, and the uterus and vagina were packed. Death occurred 2 hours later.

In multiparas hemorrhage was more severe. Of the 7 women admitted to the hospital in shock, 6 were multiparas; 4 were in labor. The significant clinical data of the only 2 cases in which severe antepartum hemorrhage occurred follow:

CASE 2. A secundigravida, aged 34 years, at term, was admitted to the hospital with pain in the chest, dyspnea and cyanosis. There was no vaginal bleeding, yet she had bled in the 34th week. Rectal examination was followed by profuse hemorrhage. Death 1 hour later, with baby undelivered, was attributed to pulmonary embolism. At autopsy, the lung condition was not significant. Complete placenta previa was present.

CASE 3. A secundigravida, aged 29 years, suffered severe initial hemorrhage 2 hours before the onset of labor in the 38th week of pregnancy. It was estimated that 2000 cubic centimeters of blood were lost in 4 hours before patient was admitted to the hospital in shock, with blood pressure 70/50 and pulse rate 150. Plasma (500 c.c.) and blood (500 c.c.) were administered. Six hours later after loss of fetal heart sounds, patient was examined vaginally and complete placenta previa was felt through a cervix which was dilated 4 centimeters. The cervix was then dilated manually and a No. 4 Voorhees bag was introduced. The patient complained of intense abdominal pain, the uterus became boardlike and shock deepened. The bag was then removed and blood (500 c.c.) and plasma (500 c.c.) were again administered. The cervix was then dilated again manually, and version and extraction of a stillborn fetus were performed through the placenta, which was then removed manually. Death on the 9th day postpartum was due to embolism, proved by autopsy.

MANAGEMENT

In no case was there record of a pelvic examination prior to hospitalization. In 4 cases rectal examination precipitated profuse hemorrhage, and in several other cases repeated rectal examination did not. Not infrequently a patient was discharged from the hospital after vaginal examination failed to reveal placenta previa, only to return later after another hemorrhage at home; upon re-examination the diagnosis was clear. In most cases blood was transfused at some time before death, yet the amounts were usually inadequate, or transfusion was performed too late. The initial management is summarized in Table III.

In every case but 1 (eclampsia) hemorrhage contributed to death, yet infection was the immediate cause of death in 19 cases, 15 of them after abdominal delivery.

TABLE III.—INITIAL MANAGEMENT

Procedure	No. of cases
Cesarean section	22
Internal version	4
Version and extraction	8
Braxton-Hicks version	4
Rupture of membranes	3
Bag alone	3
Pinard maneuver	1
Vaginal pack	1
Incision of cervix and forceps	1
Undelivered, spinal anesthesia	1
Undelivered, eclampsia	1
Undelivered, no treatment	1
Total	50

Postpartum hemorrhage and shock caused death in 23 cases, 3 after cesarean section and 20 following delivery from below. Extraction followed version in 8 cases, in 1 case after Braxton-Hicks version. A Voorhees bag preceded version in 6 of these cases. In a patient with a marginal placenta previa, the breech was extracted through a cervix dilated but 3 centimeters. In another case, delivery was effected by forceps after lateral incisions in a cervix dilated less than 3 centimeters. And a patient treated by vaginal tamponade died of postpartum hemorrhage after precipitate delivery of twins. In another case rupture of the uterus followed the Pinard maneuver.

Severe postpartum hemorrhage occurred in all of these cases. Rupture of the uterus is known to have occurred in 2 cases, while in another a deep cervical laceration was reported. In 5 additional cases, all after version, though a tear in the uterine wall was not actually palpated, it is our belief that clinical evidence will support the diagnosis of ruptured uterus. With the exception of a death from severe infection 34 hours after version and extraction, all 23 patients died within a few hours of delivery.

Fetal survival in the cesarean section group was 14 and in the pelvic delivery group 4.

DISCUSSION

In the management of placenta previa the prime indication is prevention of death from hemorrhage. Infection may not be controlled as well as hemorrhage; proper management of hemorrhage is a clear prerequisite of treatment. Death from infection occurs more commonly after cesarean section, yet many wom-

en in the pelvic delivery group may have died of sepsis if they had survived hemorrhage.

The danger of puerperal infection in a patient who has suffered excessive blood loss prior to any operative procedure is great. The presence of the placenta in the vascularized lower segment, in close proximity to the vagina which may harbor highly pathogenic organisms, favors spread of infection. And vaginal manipulation, even aspetic vaginal examination, may result in lacerations which open new avenues for infection.

It is likely that vaginal examination performed with strict asepsis just prior to cesarean section involves but little risk. If, however, this examination is preceded by vaginal examination 5 or 6 days before, risk of infection is great. However carefully examination is performed, bacteria may be carried into the bloody area of placental separation. Later examination, before infarction has taken place, will disturb an area of invasion in which bacteria are multiplying in excellent culture media.

Severe antepartum hemorrhage, in the absence of pelvic examination or other manipulation, and before the onset of labor is uncommon, occurring four times in this series. Multiparas are prone to severe hemorrhage, usually preceded by significant lesser bleedings; however, the first hemorrhage may be profuse. The character and time of bleeding episodes appear to be unrelated to the type of placenta previa.

If version has been performed, it should not be followed by prompt extraction, for hemostasis has usually been effected, and time for replacement of lost blood is a valuable asset. The indication is not delivery of the fetus, but control of hemorrhage. Extraction is particularly hazardous when the cervix is less than fully dilated, for the lower uterine segment may be ruptured. In every case the uterus should be carefully explored if version has been performed.

The high incidence of death from hemorrhage occurring during the placental stage and shortly afterward is notable. When the placenta is situated in the lower segment of the uterus, its separation is likely to be retarded and partial, and bleeding will be free. If there is no hemorrhage, expression should not be attempted until the placenta lies in the vagina. If bleeding occurs after the birth of the child, waiting for spontaneous separation and expulsion of the placenta is an invitation to hemorrhage. Manual removal should be prompt. Johnson, however, in complete disagreement "allows the placenta to separate naturally," and states that "no effort should be made to hasten separation of remaining attached placental tissue." The ease of rupture of the lower uterine segment should be borne in mind; in this series of 20 deaths from hemorrhage after pelvic delivery, 8 women died of rupture of the uterus.

Facilities for transfusion of large amounts of blood should be on the delivery floor. Failure to be prepared for replacements of lost blood is inexcusable. Plasma is hardly a worthwhile stop gap, without value if hemorrhage has been profuse, and dangerous if it is the pooled plasma so commonly used at present. The need for large amounts of blood, however, grows less with good management.

Of greater importance than blood transfusion is good judgment in selection of the time and method of treatment. Large amounts of blood may not be relied upon to save the mismanaged patient.

Macafee (4) says, and others concur, that "it would appear that a patient with placenta previa dealt with efficiently in suitable surroundings where a transfusion of blood is available should not die from hemorrhage." There was but 1 patient in this series who bled to death before transfusion or any operative procedure could be carried out.

CONCLUSIONS

In this series of 50 maternal deaths associated with placenta previa antepartum hemorrhage caused death in but 1 patient whose atypical symptoms point to a very unusual degree of abruptio associated with placenta previa.

Death was largely due to intrapartum and postpartum hemorrhage, operative trauma, and sepsis. Blood replacement was for the most part very inadequate. The dangers incident to mismanagement of delivery are far greater than the risk of prior expectant treatment.

Vaginal or rectal examination should not be performed at home. Following admission to

the hospital, after the first hemorrhage, the vagina and cervix should be inspected through a speculum which has been cautiously introduced.

In the interest of the fetus, no other vaginal examination should be performed, notwithstanding recurrent bleeding, until one decides to terminate expectant treatment, in about the 38th week of pregnancy. And then only when preparations for delivery, by cesarean section or otherwise, are complete with suitable blood replacement on the delivery floor. Vaginal examination may fail in diagnosis if the cervix is not sufficiently taken up.

Tamponade and dilating bags are obsolete, and version nearly so. As Macafee (4) says "It should be reserved for controlling severe hemorrhage when the fetus is immature or already dead." Interference from below should be restricted to rupture of the membranes; and the advantage of that procedure should be weighed if the presentation should be the frank breech. Other than rupture of the membranes, the only vaginal procedure which may be indicated is pulling down an easily accessible foot in the case of a multipara with a full breech or foot presentation.

Cesarean section will be indicated in most cases.

It should be elected without hesitation when the placenta previa is complete or partial, or type 3 and 4 according to the excellent classification rapidly finding favor in Great Britain. When the placenta is marginal (type 2) or what is unhappily called low implantation (type 1) the character of the cervix is an important factor in arriving at a decision.

Since the hazards of intrapartum and postpartum hemorrhage seriously increase the risk of death from hemorrhage, the placental stage should be carefully followed with a view to prompt manual removal of the placenta should bleeding continue after delivery of the fetus.

Expectant treatment of placenta previa is safe under proper conditions. The patient should remain in the hospital during the period of expectancy.

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ONE STAGE RESECTION AND ANASTOMOSIS OF THE COLON

A REVIEW of surgical literature of the past 5 years discloses a decided trend toward a return to primary resection and anastomosis of the colon. McKittrick in a recent (1948) comprehensive consideration of surgery of the colon wrote that "It shares with all other surgical procedures the improvement in results following the many advances in the care of patients that have occurred in recent years, tending, I believe, more nearly to standardize surgical treatment of cancer of the colon than has been possible before."

The writer, as a result of a survey by questionnaire, undertaken in 1947 to determine current trends in the surgical treatment of carcinoma of the large intestine as practiced by 50 surgeons with relatively large and prolonged experience in this field, has reached the same conclusion. Thirty-six, or 72 per cent, indicated that in at least 50 per cent of instances they elected primary resection and anastomosis as the procedure of choice. One stated that he never employs this maneuver while four claimed one hundred per cent performance. Between these extremes the varied incidence of performance was as follows: 5 to 24 per cent of cases, 7 surgeons, or 14 per cent; 25 to 74 per cent, 11 surgeons, or 22 per cent; and 75 to 100 per cent of cases, 31 surgeons, or 62 per cent. Notwithstanding this popular preference for a one stage operation, it appears significant that 6 of the 10 surgeons in our survey who are generally conceded to be pre-eminent in this field, and whose replies were tabulated separately, estimated that they performed primary resection and anastomosis in not more than 25 per cent of instances. One of these, T. E. Jones, has not anastomosed the distal colon primarily since January, 1938. During a period when most of the surgeons in the majority group, who now favor primary anastomosis, performed exteriorization procedures exclusively, he was one of the principal advocates of immediate anastomosis which he accomplished with the relatively low mortality (for that period) of 14 per cent in 128 cases. Dissatisfied, however, with this rate, he adopted the exteriorization technique of Rankin (obstructive resection) and in a series of 117 cases performed without the benefit of chemotherapy reported a mortality of only 5 per cent. Moreover, the overall hospitalization period averaged only 26 days, including the period for closure of the temporary colostomy. David employs an exteriorization operation in all but 5 to 10 per cent of cases and the Lahey Clinic in all but 10 to 15 per cent of such lesions. Rankin, Cole, MacFee, and Dixon perform primary

anastomosis in not more than 35 per cent of instances.

Although a considerable majority of those interested in surgery of the large intestine are in agreement as to the operation of choice in lesions of the distal colon, a decided difference of opinion prevails as to which factor, or factors, chiefly are responsible for the current relatively low mortality which accompanies resection and immediate anastomosis. A few, notably Dixon, Heyd, and White believe that routine establishment of complementary proximal drainage favorably influences mortality, whereas a majority (85 per cent) in the survey conducted by the writer, especially Stone, Waugh, Meyers, Wangensteen, and Campbell, have taken positive stands to the effect that such decompression as a routine measure is not essential to a low mortality in primary anastomosis. The Miller-Abbott tube was considered a valuable adjunct to resection of the distal colon by only five, whereas special merit was ascribed to the Devine colostomy by only three.

Controversy also continues concerning the comparative efficacy of the closed and open methods of intestinal anastomosis. Whipple, Meyers, and a few others have strenuously criticized the aseptic technique, particularly those which employ a special clamp. On the other hand, Stone, Rankin, Wangensteen, Waugh, White, Pemberton, Dixon, and McKittrick are among the majority (60 per cent in our survey) who believe mortality is favorably influenced by the closed technique. A similar division of opinion is found in the evaluation of chemotherapy and the antibiotics. Jones, Stone, Lahey, Cattell, Coller, Wangensteen, Gurd, McKittrick, and a few others use them not at all or only rarely. However, most surgeons (84 per cent in our survey) consider these agents important adjuvants in primary anastomosis of the colon and utilize them routinely. The extremes are represented on the one hand by Jones who never employs chemotherapy in any form and on the other by Pemberton who feels that the part played by chemotherapy in the reduction of mortality in surgery of the colon is "as spectacular and revolutionary as the changes wrought by iodine therapy in surgery of exophthalmic goiter." Actually, there have not been reported sufficiently large series of cases to permit accurate evaluation of the favorable influences of any one therapeutic agent or technical maneuver. More likely, as recently emphasized by Allen, Ravdin, McKittrick, and others, a combination of factors have contributed to the improved results as: (1) a better understanding and utilization of preoperative preparation, especially as regards anemia and serum protein deficiency; (2) improvement in anesthetic methods; and (3) the advent of chemotherapeutic agents for oral use during the preoperative period.

It is also difficult properly to determine the relative merits of obstructive resection and primary resection and anastomosis in the treatment of cancer of the colon prior to the publication of large series of cases in which are included such revealing data as operability, mortality, and five year survivals. The fallacy of attaching significance to statistical consideration of a limited number of cases such as have been recently reported has been demonstrated frequently. Initial series of cases usually consist of carefully selected patients and as a consequence mortality is lowest for the first score or so of operations.

MacFee, long an advocate of primary anastomosis as the procedure of choice, recently aptly expressed the concern with which a number of us have viewed the all-or-none

attitude adopted by many surgeons in regard to primary suture of the distal colon after resection. He says "When primary resection is intended and an unforeseen complication is encountered, there is always the inclination to proceed with the definitive operation as planned, bearing in mind, but at the same time disregarding, the fact that conditions for the operation are not ideal. The results may be chastening to the surgeon and irreparably bad for the patients. It is the middle ground cases that offer the greatest temptation and, therefore, the greatest danger."

A. STEPHENS GRAHAM.

PANCREATIC PHYSIOLOGY IN THE LIGHT OF RECENT SURGICAL EXPERIENCES

THE surgery of pancreatic neoplasms as developed in recent years has afforded considerable opportunity for the study of pancreatic physiology. Previously, much that was taught concerning the pancreas was based upon observations made in the laboratory upon various types of animals; the inference was that the facts thus gleaned in all probability applied to human beings. Recent surgical experiences, however, would indicate that human pancreatic physiology differs in certain respects from that observed in the several varieties of laboratory animals.

In a recent publication[1] dealing with the etiology of acute pancreatitis as observed in cats and produced by ligation of the main ducts and stimulation of the gland by feeding, it is concluded that the most important factor is obstruction of the ducts. Neoplasms of the head of the pancreas or ampulla produce high grade obstruction of the ducts and these patients rarely exhibit concomitant acute pancreatitis, although prior to operation the obstruction did exist and there was stimulation when the patients ingested food. Furthermore, pancreatoduodenectomy without implantation of the transected neck into the jejunum, is in effect a ligation experiment in man and the operation is not followed by acute pancreatitis when the patient recovers, the fistula is closed and the gland is stimulated by ingestion of food.

In the earlier phases of the development of pancreatic surgery, the question was frequently asked by internists, physiologists, and others why the patients did not develop acute pancreatitis. Why they should be expected to do so is not clear but prior teaching certainly gave a widespread impression that there would be great hazard in surgical manipulation of the pancreas. It would appear that this complication is so unusual that no surgeon now hesitates to attack the pancreas for fear of acute pancreatitis.

In the experience of the writer, operative trauma to the dog's pancreas is very well tolerated indeed, and attempts, by mashing the gland *in situ*, to produce the homologue of the large posttraumatic pseudocysts in these animals that are observed in man following crushing trauma to the upper abdomen have been negative.

Another interesting observation in man has been the variation in character of the stool following complete occlusion of the external secretion as a result of pancreatoduodenectomy without reimplantation of the transected neck of the gland. The stools are fatty, bulky, and relatively frequent in some of the patients but by no means all of them. In one case there was steatorrhea and after operation where only the bile was returned to the alimentary tract the stools were normal. In another instance, normal nutrition has been maintained for two years, in another for

[1]Linn, R., and Maddock, Stephen, Surgery, 1948, 24: 593.

four years, in a third for five and a half years,[2] in still another patient, eight years,[3] where the pancreatic juice has been completely occluded. A ready explanation is that accessory pancreases must exist to afford the external secretions but in the absence of final proof of this, other theories, such as the presence of secretions from other parts of the bowel that sometimes can substitute for pancreatic juice, are just as valid and possibly more thought provoking.

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The patients who have received total pancreatectomy afford excellent opportunities for study of carbohydrate metabolism in general. An example is the arresting observations that the totally depancreatized human requires relatively modest doses of insulin, less than in many of those who are spontaneously diabetic with the entire pancreas *in situ*. Furthermore, total pancreatectomy in the diabetic subject does not result in appreciable increase in the severity of diabetes. These facts suggest new avenues for further study of diabetes mellitus in man.

ALEXANDER BRUNSCHWIG.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE Swedish School of Radiology, developed under the beneficent direction of the universally beloved Gosta Forssell, has grown into one of the best radiological centers in the world, one which has contributed in a very large manner to the advancement of medicine in general and of radiology in particular. The new discoveries and techniques in radiology emanating from this school have been published in the various radiological journals, particularly in the *Acta radiologica* and the supplementary volumes of the *Acta* which have now reached more than sixty-five in number.

The present series of lectures, *Roentgen Studies of the Lungs and Heart*[1] by Nils Westermark, M.D., delivered at the Center of Continuation Studies of the University of Minnesota at the instigation of Professor Leo G. Rigler, integrates anatomy, physiology, pathology, and clinical medicine in the application and interpretation of roentgen diagnostic procedures most useful in the study of the heart and lungs. This is a valuable collection of dissertations very much worth study at the hands of internists, pathologists, cardiologists, and radiologists.

JAMES T. CASE.

THE book *General Endocrinology*[2] by Turner was written primarily for students who are concentrating on experimental biology rather than for the practicing physician or medical specialist. The discussion of each gland includes comparable structures in lower vertebrates and invertebrates which greatly add to the value of the book. There is sufficient gross and microscopic anatomy to permit review of the important aspects of the glands. The review of developmental and comparative anatomy certainly adds to the interest and understanding. The biochemistry of each hormone and its physiological effects are well treated and finally the results of over or under secretion are touched upon. The interrelationship of the several endocrine glands has been sufficiently stressed. Perhaps one of the book's best features is the generous reference to the classical experiments which have been done in the various fields.

The bibliography at the end of each chapter is excellent as it contains all the important references on the subject.

While this book was prepared chiefly for the student, general medical practitioners and specialists in endocrinology will find it interesting and helpful. It is well organized and well presented and is recommended to all interested in medicine and its allied fields.

BROCK BRUSH.

THE present edition of *Recent Advances in Surgery*[3] by Harold C. Edwards is the third edition of a series formerly edited by Sir Henage Ogilvie, the last published in 1929. A volume of 495 pages, well printed with numerous illustrations, it will be found of great interest to the general surgeon.

There are seven parts. The first deals with the general problems of wound healing, shock, burns, fluid balance, and antibacterial therapy. The second is particularly well done, on the alimentary system. There are notably good sections on the esophagus and on the rectum. The third part by R. C. Broch covers the thorax. The fourth by D. W. C. Northfield reviews the nervous system, with a section on head injuries, and another worth noting on intracranial aneurysms. The fifth is concerned with blood vessels and anticoagulants. The sixth summarizes the advances in the ductless glands, including prostate and breast. There is an illustrated description of Millin's operation for prostatic hypertrophy. The seventh and last part by Sir Stanford Cade is an excellent review of radiotherapy in malignant disease.

There is so much material that one may wonder how it is compressed For example in the section on the thorax, after a short introduction, the surgery of the heart is described, including wounds, foreign bodies, suppurative pericarditis, constrictive pericarditis, mediastino-pericarditis, congenital abnormalities, pulmonary atresia, angina pectoris, extracoronary and intercoronary communications. A detailed chapter follows on bronchial carcinoma. And, at the end of each chapter, an adequate list of references will be found. An index also follows at the end of the book.

This book is very readable, and it can be recommended to those who would review these fields. It differs from our Year Book in that it covers a longer period and a smaller field. Referring to it one can be assured of a summary of the advances in each field and a list of important references.

JOHN L. ATLEE, JR.

[1] ROENTGEN STUDIES OF THE LUNGS AND HEART; A SERIES OF LECTURES DELIVERED AT THE CENTER FOR CONTINUATION STUDY, UNIVERSITY OF MINNESOTA. By Nils Westermark, M.D. Edited by Leo G. Rigler, M.D. Minneapolis: The University of Minnesota Press, 1948.

[2] GENERAL ENDOCRINOLOGY. By C. Donnell Turner, Ph.D. Philadelphia and London: W. B. Saunders Co., 1948.

[3] RECENT ADVANCES IN SURGERY. By Harold C. Edwards, C.B.E., M.S., F.R.C.S. 3rd ed. Philadelphia: The Blakiston Co., 1948.

TO those interested in the preparation and publication of scientific papers, *Medical Writing*,[1] by Morris Fishbein, Editor, and Jewel F. Whelan, assistant to the Editor of the *Journal of the American Medical Association*, will be found most useful. The book contains a wealth of valuable information and the very full index makes this information easily accessible. One might wonder why pains were taken to spell out the captions to Figure 12, B, in the chapter on illustrations, in letters so black and ungainly as to focus attention on them rather than on the drawing itself. Some of the rules given for the copy-editing of manuscripts for American Medical Association publications might be considered arbitrary but the publications of the Association speak for themselves as to the high quality of the work the Association does. *Medical Writing* should be of great help to the doctor preparing a manuscript, to his secretary who copies it, and to the copy editor whether or not associated with the American Medical Association.

M. E. SPENCER.

THE volume by Dr. R. B. H. Gradwohl *Clinical Laboratory Methods and Diagnosis*[2] has increased in size with every edition until now in the fourth edition it fills three large volumes and more than 3,300 pages. It is encyclopedic in scope and modern in content. In addition to the chapters which describe all the tests which are performed in the ordinary day's work of a large hospital laboratory, there are also comprehensive sections on electrocardiography, autopsy technique, toxicological methods, and the detection of crime by laboratory methods. The entire third volume, which is written in collaboration with Dr. Pedro Kouri of the Faculty of Medicine of Havana University, is devoted to parasitology and tropical medicine and is noteworthy for the pictures illustrating the pathology of the various diseases.

The general plan of the book includes a detailed description of nearly all the modifications of the different laboratory procedures, which is followed by a discussion of the interpretation of the results. Frequent lengthy accounts of certain clinical and therapeutic aspects of the diseases under discussion are also included. A commendable feature is the detailed description of the various scientific instruments which are used in the laboratory. Each manufacturer's instrument, although frequently designed on the same basic physical or chemical principles, often requires minor but essential variations of operation and it is helpful to have these differences explained.

There is a good discussion of the cytological diagnosis of cancer of the uterus, bronchus, and prostate by the methods of Papanicolaou, of Ayre, and Dakin, and of others followed by an even better evaluation of the results of this method of diagnosis. The illustrations for this section of the book are especially fine, and for the most part are reproduced from articles which appeared in SURGERY, GYNECOLOGY AND OBSTETRICS.

This book will undoubtedly be used constantly as a guide in many laboratories and should prove a ready aid to the experienced as well as the inexperienced laboratory worker. This reviewer, however, would like to suggest that future editions could be considerably shortened by critical editing of the material which is included in the book and the use of an economical literary style. Much chaff could be winnowed from the wheat.

WILLIAM B. WARTMAN.

THE sixth edition of *Recent Advances in Anaesthesia and Analgesia*[3] by C. Langton Hewer was designed to present information regarding recent developments in anesthesiology. The small, concise volume deals briefly with basic principles and new topics. Prominence is given to the use of curare and similar drugs as specific muscle relaxants. Numerous references are listed at the end of chapters and many illustrations of equipment are included.

Of particular interest are the chapters which take up psychological aspects and theoretical considerations of anesthesiology. Special attention is given to charts and records with emphasis on the card index systems. The discussion of trilene is of value as this noninflammable agent is little known in this country. The use of anesthesia in domiciliary practice is a field in which most American anesthetists lack experience. The author had extensive wartime work with cases of trauma, and his remarks regarding the administration of anesthesia to patients in shock are well worthwhile.

Considerable space has been devoted to mention of experimental, infrequently used, and obsolete drugs. The discussion of shock therapy quickly dismisses blood transfusion but provides a conspicuous list of analeptics. The use of ethyl chloride analgesia for short dental operations seems a hazardous procedure due to the cardiac effects of this potent drug. It is stated that nitrous oxide anesthesia is used extensively in the United States for major surgery; this secondary saturation technique has been discarded by most because of the anoxia involved.

The text is general in treatment, and no technical details are given for the most part. The subject matter includes such fundamental topics as premedication, agents and methods of anesthesia, apparatus, explosion hazards, oxygen therapy, and anesthetic management of various types of surgical cases. The student will find the basic principles of anesthesiology briefly outlined. The specialist will note some points unfamiliar to American practitioners. However, the primary interest of this book is its presentation of the British viewpoint in the practice of anesthesiology.

MARY FRANCES POE.

[1] MEDICAL WRITING, THE TECHNIC AND THE ART. By Morris Fishbein, M.D. 2nd ed. Philadelphia and Toronto: The Blakiston Co., 1948.

[2] CLINICAL LABORATORY METHODS AND DIAGNOSIS; A TEXTBOOK ON LABORATORY PROCEDURES WITH THEIR INTERPRETATION. By R. B. H. Gradwohl, M.D., D.Sc., F.R.S.T.M.&H. (Lond.). Volumes 1, 2, 3. 4th ed. St. Louis: The C. V. Mosby Co., 1948.

[3] RECENT ADVANCES IN ANAESTHESIA AND ANALGESIA. By C. Langton Hewer. 6th ed. Philadelphia and Toronto: The Blakiston Co., 1948.

AN amplification of the author's earlier book, *Diseases of the Ear, Nose and Throat*[1] by William Wallace Morrison includes the same type of anatomic and histopathologic line drawings which clarified that excellent text.

This is no exhaustive rehash of abandoned theories; it presents up to date findings and is documented with references to recent work at the end of each chapter. Valuable diagrams of endaural surgical procedures, including fenestration, excellent discussions of nasal allergy and of headaches, and of tracheobronchial neoplasms, have been added. There is an extensive formulary of medicaments for patients, and a valuable symptom index.

As a guide for the general practitioner and a ready reference work for the specialist in this field, Morrison's book cannot be surpassed.

RALPH A. FENTON.

IN the third edition of *Essentials of Pathology*[2], Smith and Gault have maintained the standard of the two previous editions and have made a number of changes which are worthy of mention. The photomicrographs are clearer, more numerous, and are selected to demonstrate the more common lesions. A similar comment may be made about the photographs of gross specimens and the roentgenograms. It is suggested that the colored plates on malarial parasites, the various cells of the hematopoietic system, and the eye grounds could be supplanted by colored plates of true pathologic changes. The former ones are ordinarily seen in manuals of clinical medicine.

Discussion still continues on the use of the case method of teaching. Since it remains of questionable value in teaching pathology, the authors are wise in condensing the case histories used in this volume. Many unnecessary words and phrases have been eliminated without detracting from the clarity of the explanations.

A proper increase in the amount of space allotted to neoplasms has been made. The sections on the bacterial and the parasitic diseases are still the best in their respective divisions of any of the commonly used texts of pathology. In a future edition, there could be added chapters on the pathology of skin and of the special senses. This would enhance its value and enable the student to be grounded in the pathologic changes of the more common entities seen in these specialties. Consideration might also be given to the possible inclusion of a section on radiation effects.

The two column format of the printed page makes reading less fatiguing, more accurate, and more rapid. This volume may be wisely used by the student and practitioner either for preliminary study or as a review of the fundamentals of pathology.

MARK WHEELOCK.

[1]DISEASES OF THE EAR, NOSE AND THROAT. By William Wallace Morrison, M.D. New York: Appleton-Century-Crofts, 1948.

[2]ESSENTIALS OF PATHOLOGY. By Lawrence W. Smith, M.D., F.C.A.P., and Edwin S. Gault, M.D., F.C.A.P. 3rd ed. Philadelphia and Toronto: The Blakiston Co., 1948.

CHRISTOPHER'S *Minor Surgery*[3] is so well known and so widely used that little needs to be said concerning the general content of the volume. The scope of the book, according to the preface, is the consideration of the pathogenesis, diagnosis, and treatment of conditions which are included in the surgical operations performed by the general practitioner, by the physician who does not have ready access to large hospitals or contact with specialists in surgery and by the physician who was unable to serve the long apprenticeship necessary for the practice of surgery. A sincere effort has been made to avoid provincialism. Direct quotations are used extensively, an excellent method by which to present the ideas of experts in a particular field and, as the author points out, the fairest method of giving credit to these men. In addition, the method serves admirably to introduce many leaders in surgery, through some of their best work, to surgical intern and resident.

The first three chapters deal with wounds and infections, and the succeeding four chapters deal with burns, foreign bodies, injuries by electricity, and circulatory disturbances. Subsequent chapters discuss injuries, infections, deformities and tumors of the head, neck, trunk and extremities. The male and female genitourinary organs are covered in separate chapters and the valuable sections pertaining to preoperative and postoperative care, minor surgical technique, and the duties of the surgical intern have been retained.

One might be somewhat skeptical as to the necessity of another edition four years after publication of the fifth edition but in reading this volume the reviewer concluded that the sixth edition is amply justified by the author's continued effort to supply information of latest advances and most approved methods of treatment. The length has been increased by approximately fifty pages. The paper, typography and binding are excellent, as are most of the illustrations. References have been moved from footnote position to the ends of the various chapters. The incredible number of references is a gauge of the extensive coverage of the field and the merit of the volume is greatly enhanced by the bibliography. For example, there are 451 references, designated by number, in the chapter on open wounds. The criticism may be carping but, with references at the end of the chapters, one would prefer to have them arranged in alphabetical order. While this edition has been extensively revised, the general format remains unchanged.

As would be expected, in fields in which considerable progress has been made extensive revision has been necessary, and several new sections have been added. The discussions of antibiotics and sulfonamides have been greatly expanded, as have the sections on thrombophlebitis, phlebothrombosis, burns, varicose veins and pilonidal cysts. New material, in this edition, includes information concerning gelatin

[3]MINOR SURGERY. By Frederick Christopher, B.S., M.D., F.A.C.S. 6th ed. Philadelphia: W. B. Saunders Co., 1948.

sponges and oxidized cellulose, early postoperative ambulation, Lund's tables of skin areas, excision and closure of bedsores, treatment of malignant melanoma, placement of neck incisions, refrigeration anesthesia as well as consideration of other recent advances. Other sections have been extensively amplified, particularly those dealing with wound healing; certain fractures and sprains; skin grafting, with a discussion of the Padgett dermatome; blood transfusions; the Rh factor, and fluid and electrolyte balance.

The sixth edition, with revisions and additions of material, is the best book in its field.

B. MARDEN BLACK.

FOR his recent book Dr. Walter has taken the same title which Schimmelbusch used in 1892, namely, *The Aseptic Treatment of Wounds*.[1] The difference in the size and scope of these two books is indicative of the progress that has been made in this field in the last 56 years. The introductory chapters show graphically the contributions made during the overlapping careers of many different men and the gradual evolution of the philosophy of asepsis over a period of two hundred years from Charles White to Johann von Mikulicz-Radecki, the former stressing cleanliness and isolation and the latter emphasizing the importance of masks and gloves and the dangers of wound contamination from the air.

Dr. Walter has brought to this problem his early technical training, which he has applied to the mechanics of sterilization of dry goods, instruments, solutions, nay more the whole environment of the operative field. He has stressed the belief that the surgeon himself should understand these principles, in order that he may direct and control these processes rather than turn the responsibility over to a constantly changing personnel among his assistants. However, the book is written not only for the surgeon but for the technical assistants in the operating room, so that they too may understand the necessity for the minutiae of detail required to prevent the entrance of bacteria into the wound of the patient, particularly those which may come from the mechanical devices involved in sterilization.

In his delineation the author is greatly aided by the excellent line drawings of his co-author, Mildred Codding, who with keen understanding follows through the steps of the preparation of the patient, the personnel and the sterile field, clearly illustrating the closing and opening of laparotomy kits, surgical drapes, surgical gowns, pads, masks, and the arrangements of instruments.

The book stresses the importance of the controls required to make foolproof the steam sterilization both for routine and emergency work and the care of the instruments both before and after this procedure. The rationale of the surgical scrub-up, both for the doctors' hands and for the operative field, is thoroughly explained. The dangers of contamination by air-borne bacteria are carefully considered, with special reference to the bacteria which are brought in by the operating personnel on their clothing and shoes and particularly in their noses and throats, from which organisms can so readily be distributed to the sterile field or into the wound, where they may grow rapidly because they have come so recently from a similar human environment.

In the operating room technique itself Walter stresses the importance of team work and here Mildred Codding comes to his aid with innumerable illustrations which should be of great value to any operating room staff which desires to work with optimum efficiency and safety.

The book lays special stress on the terminal sterilization of instruments and textiles from septic cases which are potential sources of bacterial contamination. Their care is often neglected in many hospitals. Contamination from this source can be reduced to a minimum by the intelligent application of the principles involved. This danger can be controlled almost single handed by a conscientious scrub-up nurse.

Dr. Walter goes into the necessity for great care in the preparation of parenteral fluids, including blood and plasma, and the importance of the avoidance of reactions from the administration of these fluids.

The author also emphasizes the value of carrying the principles of asepsis into the wards where daily dressings are done, in order to avoid the spread of infection from one patient to another and the transfer of organisms from patients to attendants and attendants to patients. This also is an important phase of asepsis which is often neglected. It has recently been re-emphasized during the war period when soldiers were brought into hospitals in great numbers, carrying with them the contamination from the fields of battle as well as the organisms causing nonsurgical communicable diseases.

I have no hesitation in saying that this book should be part of the equipment of every hospital operating room and be read and understood by every surgeon and his assistants. FRANK L. MELENEY.

IN these days of "schools" of psychiatry, with each group supported by zealous followers who believe that only their method is correct, it is difficult to prepare a book of psychiatry which would not be confusing to the uninitiated. Certainly the medical student, completely unaware of different philosophies and ideologies in a rapidly expanding specialty, can develop no well organized concept of human behavior and its aberrations when this difficult subject is presented from so many different angles.

It is gratifying, therefore, to read the book *Modern Clinical Psychiatry*[2] which had been established earlier as a textbook and find the entire subject of psychiatry treated temperately, yet extensively and comprehensively. Dr. Noyes himself is apparently a follower of Adolph Meyer and his philosophy of psycho-

[1] THE ASEPTIC TREATMENT OF WOUNDS. By Carl Walter, A.B., M.D. Illustrated by Mildred B. Codding, A.B., M.A. New York: The Macmillan Co., 1948.

[2] MODERN CLINICAL PSYCHIATRY. By Arthur E. Noyes, M.D. 3d ed. Philadelphia and London: W. B. Saunders Co., 1948.

biology, but he reviews all the earlier contributions of Kraepelin, Bleuler, Janet, and finally culminates in a complete objective evaluation of the psychoanalytical theory of behavior and its applicability in therapy. The different spheres of thought are handled in such a way as to leave the student clear as to what is definitely established.

At the same time the practical aspect of the applicability of the various regimens of treatment is not lost sight of. The book contains comprehensive chapters on institutional care, special procedures like hydrotherapy, occupational therapy, recreational therapy and psychotherapy, plus the more recent methods of insulin and convulsive shock therapy. The treatment of neurosyphilis by fever and penicillin is discussed comprehensively. Even frontal lobotomy is evaluated. A chapter is included on psychosomatic medicine in which the relationship of psychiatry to general medicine is well delineated. Psychotherapy is reviewed in its various disciplines. The closing chapter is on child psychiatry which gives the reader an idea of some of the disturbances that may be encountered in the young.

All in all the author covers the field of psychiatry in a broad manner. His own experience and background are such as to enable him to have a mature opinion about the various techniques of the care of the mentally ill, and with many of the therapies like shock therapy and the fields of psychotherapy beginning to come of age, an objective measure can be made and is presented.

I enjoyed reviewing this book and can recommend it for medical students and for general practitioners. It is a book that could well be frequently used by every psychiatrist, no matter what his personal philosophies. BENJAMIN BOSHES.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

LIVES OF MASTER SURGEONS. By Richard A. Leonardo, M.D., Ch.M., F.I.C.S. New York: Froben Press, Inc., 1948.

CONDITIONED REFLEXES AND NEURON ORGANIZATION. By Jerzy Konorski. Translated from the Polish under the author's supervision by Stephen Garry. Cambridge, University Press; New York: The Macmillan Co., 1948.

L'ADENOMECTOMIE PROSTATIQUE RETRO-PUBIENNE. By R. Couvelaire. Paris: Editions Bernard Baschet, 1948.

HEMATOLOGY. By Cyrus C. Sturgis, M.D., Springfield, Ill.: Charles C Thomas, 1948.

SURGICAL PATHOLOGY. By Peter A Herbut, M.D. Philadelphia: Lea & Febiger, 1948.

ENDOGENEOUS ENDOCRINOTHERAPY INCLUDING THE CAUSAL CURE OF CANCER COMPENDIUM. By Jules Samuels, M.D. Amsterdam, Netherlands: Holdert & Co., 1948.

AFFECTIONS MÉDICALES ET CHIRURGICALES DU PIED. By Raphaël Massart. Paris: G. Doin & Co., 1948.

PATHOLOGIA DA GESTACAO. By Professor Raul Briquet. Sao Paulo: Editora Renascenca, S.A., 1948.

AN INTRODUCTION TO GASTRO-ENTEROLOGY. By Walter C. Alvarez. 4th ed. New York: Paul B. Hoeber, Inc., 1948.

EMERGENCY SURGERY. Parts 1 and 2. By Hamilton Bailey, F.R.C.S. (Eng.), F.A.C.S., F.I.C.S., F.R.S.E. 6th ed. Baltimore: The Williams & Wilkins Co., 1948.

THE CLINICAL MANAGEMENT OF VARICOSE VEINS. By David Woolfolk Barrow, M.D. With foreword by Arthur W. Allen, M.D. New York: Paul B. Hoeber, Inc., 1948.

HISTOPATHOLOGY OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS. By George B. Hassin, M.D. 3d rev. enl. ed. Chicago: The Author, 1948.

CLINICAL UROLOGY. ESSENTIALS OF DIAGNOSIS AND TREATMENT. By Lowrain E. McCrea, M.D., F.A.C.S., F.I.C.S. 2d ed. Philadelphia: F.A. Davis Co., 1948.

PREMATURE INFANTS; A MANUAL FOR PHYSICIANS. By Ethel C. Dunham, M.D. Washington: Federal Security Agency, Children's Bureau, 1948.

CONTROL OF PAIN IN CHILDBIRTH. By Clifford B. Lull, M.D., F.A.C.S., F.I.C.S., and Robert A. Hingson, M.D., F.I.S.C., F.A.C.S., F.I.C.A. With an introduction by Norris W. Vaux, M.D. 3d ed. Philadelphia: J. B. Lippincott Co., 1948.

POSTURE AND NURSING. By Jessie L. Stevenson, R.N., P.T. 2d rev. ed. New York: Joint Orthopedic Nursing Advisory Service of the National Organization for Public Health Nursing and the National League of Nursing Education, 1948.

ATLAS OF HUMAN ANATOMY; DESCRIPTIVE AND REGIONAL. By M. W. Woerdeman, M.D., F.R.N.A. Sc. Vol. 1—OSTEOLOGY, ARTHROLOGY, MYOLOGY. Baltimore: The Williams & Wilkins Co., 1948.

TEXTBOOK OF GENITO-URINARY SURGERY. Edited by H.P. Winsbury-White, M.B., Ch. B., F.R.C.S. (Edin.), F.R.C.S. (Eng.). Baltimore: The Williams & Wilkins Co., 1948.

THE PARATHYROID GLANDS AND METABOLIC BONE DISEASE; SELECTED STUDIES. By Fuller Albright, A.B., M.D., and Edward C. Reifenstein, Jr., A.B., M.D., F.A.C.P. Baltimore: The Williams & Wilkins Co., 1948.

THE MODERN MANAGEMENT OF GASTRIC AND DUODENAL ULCER. Edited by F. Croxon Deller, M.D., M.R.C.P. Baltimore: The Williams & Wilkins Co., 1948.

THE FRONTAL LOBES; PROCEEDINGS OF THE ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE. Edited by John F. Fulton, M.D., Charles D. Aring, M.D., and S. Bernard Wortis, M.D. Vol. 27. Baltimore: The Williams & Wilkins Co., 1948.

THE SURGERY OF THE STOMACH AND DUODENUM. By T. H. Somervell, M.A., M.B., B. Ch. (Cantab.), F.R.C.S. (Eng.). Baltimore: The Williams & Wilkins Co., 1948.

TECHNIQUES CHIRURGICALES VAGINALES. By Eric Weber. Paris: J. B. Baillière & Fils, 1948.

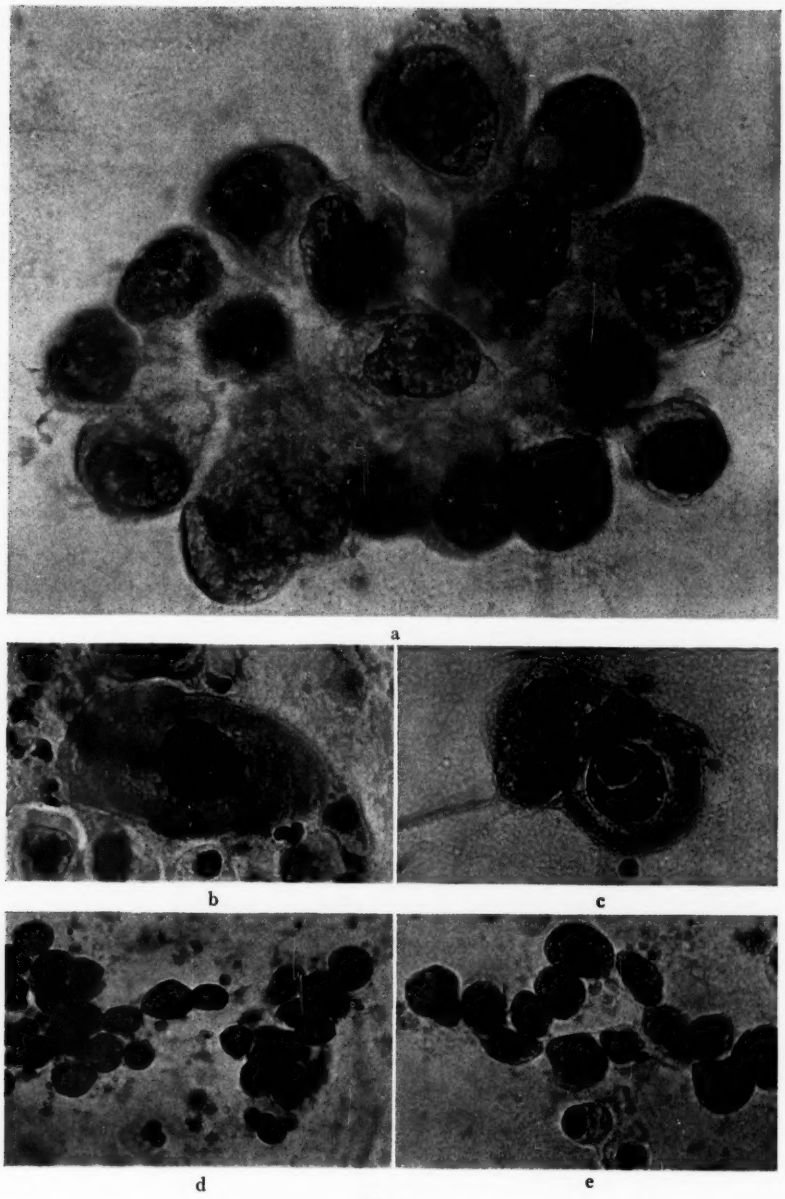

Fig. 4.

Carcinoma Cells in Sputum and Bronchial Secretions. A Study of 150 Consecutive Cases in Which Results Were Positive.—Lewis B. Woolner and John R. McDonald.

(*Legend on opposite page.*)